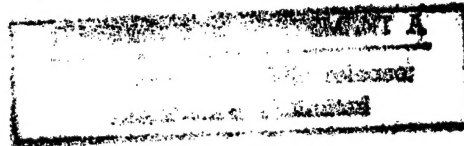


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LIFE SCIENCES

BIOMEDICAL AND BEHAVIORAL SCIENCES

No. 22

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29 September 1982

USSR REPORT
LIFE SCIENCES
BIOMEDICAL AND BEHAVIORAL SCIENCES

No. 22

CONTENTS

BIOCHEMISTRY

Conference of Young Specialists in Medical Virology.....	1
Agricultural Productivity Enhanced By Microbial Products.....	4
HgaI Restriction Nuclease-Cleavable Oligonucleotide Adaptors: Use in DNA Synthesis.....	8
Construction and Properties of Vector for Cloning Promotor-Containing DNA Fragments: Cloning of E. Coli and Phage T7 Promoters.....	9

ENVIRONMENT

Environmental Hygiene As Related to Use of Chemistry in Agriculture.....	10
Chemical Composition of Bottom Deposits and Migrating Forms of Trace Elements They Contain.....	17

EPIDEMIOLOGY

Hemorrhagic Fever Outbreak With Renal Syndrome.....	21
Epidemic Manifestations of Natural Foci of Tick-Borne Encephalitis and Its Prevention in USSR.....	21
Probability of Infection With Tick-Borne Encephalitis in Lesser Khingan Mountains and Northern Amur Region.....	22
Reproduction of Powassan and West Nile Viruses in Mosquito Aedes Aegypti in Vivo and in Vitro in Cell Culture of the Viruses.....	23

Infectivity of Farmstead Populations of Tick Ornithodoros Papillipes Bir. With Agent of Tick-Borne Relapsing Fever in Uzbekistan.....	23
Direct Counting Method for Borrelia and Other Blood Parasites.....	24
Experimental Transmission of Visceral Leishmaniasis to Golden Hamster By Sandflies Phlebotomus Longiductus Parr. 1928 and Ph. Smirnovi Perf. 1941.....	24
Hydrogeologic Indicators in Identification of Stable Enzootic Plague Foci.....	25
Persistence of Genes of Epidemic Viruses in Natural Influenza A Populations.....	25
GENETICS	
Development of Medical Genetics Under 11th Five-Year Plan and Introduction of Its Advances to Practice.....	26
Genetic Epidemiological Approaches to Investigation of Multifactorial Diseases in Psychiatry.....	34
Co-Transfer Efficiency of pAP38, pAP39, pAP41, pAP42 and pAP43 Sex Factors.....	39
MEDICAL DEMOGRAPHY	
Public Health: Trends and Research Tasks.....	40
MEDICINE	
Computer Use for Analysis of Polyclinic Service Performance.....	50
Report About Sixth International Symposium on Electrostimulation.....	53
Current Conceptions of Pathogenesis of Botulism.....	56
Methodological Approaches to Determining Emergency Medical Care Requirements of Residents of Moscow.....	62
Organization of Control of Venereal Diseases in Moscow Oblast.....	66
Hepatic Lipogenesis in Experimental Burns.....	70
Effects of Prednisolone Therapy on Course and Outcome of Hemorrhagic Fever With Renal Syndrome.....	70

Acid-Base Balance and Electrolyte Metabolism in Patients With Hemorrhagic Fever and Renal Syndrome.....	71
Effects of Antioxidants on Burn Wound Regeneration.....	71
New Collagen Solution-Based Dressing for Burn Wounds.....	72
Hemosorption in Burn Patients.....	72
New Scheme for Clinical Periodization of Burns.....	73
Computer-Based Detection of Nonakhlazin-Induced Changes in Cardiac Adaptive Reserves in Alcoholics.....	73
Semithin Section Study of Gunshot Wound Healing.....	74
Difficulties in Differential Diagnosis Between Brucellosis and Subacute Septic Endocarditis.....	74
Lesions of Nervous System in Salmonellosis.....	75

MICROBIOLOGY

Isolation, Study and Identification of Alpha- Methylstyrene Degrading Micoorganisms.....	76
Role of Proteolysis in Reproduction of Human and Animal Viruses and Antiviral Activity of Protease Inhibitors.....	76
Cytogenetic Aspects of Production and Action of Human Interferon.....	77

PHARMACOLOGY

Plants as Sources of Biologically Active Substances.....	78
Antihypoxic Effects of Gutimin in Experimental Therapy of Acute Chlorofos Poisoning.....	87
Optimization of Schemes for Use of Interferon Inducers.....	87
Modification of Fenibut and Diazepam Effects By GABA Receptor Blocker Bicuculline.....	88

PHYSIOLOGY

Effect of Indigenous and Climate Factors of Extreme North on Human Cardiovascular System.....	89
Vitamin C Adequacy in Seamen Cruising at High Latitudes.....	94
Extent of Selectivity of Neurogenic Effects..-.....	97

Effects of Calcitonin and Somatotropin on Bone Under Hypokinetic Conditions.....	102
Effects of Short-Term Repetitive Hypoxic-Hypercapnic Exposures on Functional Adaptability of Human Respiratory and Cardiovascular Systems.....	102
Biochemical Aspects of Mechanism of Action of Cholinolytics on Brain.....	103
RADIATION BIOLOGY	
Validation of Hygienic Standards for Ionizing Radiation.....	104

BIOCHEMISTRY

UDC 578:061.3(47+57)"1981"

CONFERENCE OF YOUNG SPECIALISTS IN MEDICAL VIROLOGY

Moscow VOPROSY VIRUSOLOGII in Russian Vol 27, No 2, Mar-Apr 82 pp 125-126

[Article by V. V. Khozinskiy and M. A. Zaval'nyy, Moscow]

[Text] A conference of young specialists in medical virology, dedicated to the 111th anniversary of V. I. Lenin's birthday, was held from 14 to 17 Apr 1981 at the Institute of Poliomyelitis and Viral Encephalitides, USSR Academy of Medical Sciences. Participating in the conference were young specialists from various cities in the Soviet Union, as well as from Hungary, East Germany, Rumania and Czechoslovakia. Welcoming speeches were delivered by N. V. Komissarova, Secretary of the Gagarinskiy Raykom [Rayon Committee] of the Komsomol, I. K. Nikitin, representative of the USSR Ministry of Health, and S. G. Drozdov, Director of the Institute of Poliomyelitis and Viral Encephalitides, USSR Academy of Medical Sciences, and corresponding member, USSR Academy of Medical Sciences.

The conference program included the following topics: 1) viral morphology, biochemistry and genetics; 2) interferon and the chemotherapy of viral infections; 3) methodological bases for isolating and cultivating tissues and cytopathology; 4) natural-focal viral infections; 5) enteroviral infections; 6) vaccinal prevention, clinical picture and diagnosis of viral infections. A separate session was devoted to each of these topics. A total of 40 reports and 31 poster communications were presented. The first session heard S. B. Stefanov's general report, "V. I. Lenin and the Structure of Scientific Knowledge," which examined several conclusions from the formula "from contemplation through abstraction to practice--this is the way for knowledge of the truth."

A. G. Andzhaparidze (Moscow) presented the results of an immunoelectron microscopic examination of hepatitis A virus reproducing in cell culture. In addition to the typical particles, the author isolated in viral preparations smaller virus-like particles that reacted weakly with specific serum. These results correlated with data obtained in an examination of the liver of healthy monkeys. An original model of the structure of hepatitis B virus was presented by M. Pechek and G. Stikhi (Bucharest). E. Pokhla (Budapest) developed a method for isolating pure surface antigen of this virus. V. I. Khuastov

(Moscow) showed that the most adequate model of the virion inner capsid is a model with a triangulation number $T = 13$. The communications of V. N. Lyapustina et al. (Moscow) were devoted to studying the translation of the flavivirus genome in a cell-free system. Study of the translation products of the genome of the Russian tick-borne encephalitis virus in vitro and in vivo made it possible to elucidate the mode of production of viral structural proteins and, also, to map them on the viral genome. Of great interest was the work of Yu. A. Kazachkova and Yu. V. Svitkina (Moscow), which presented the results of mapping the proteins of encephalomyocarditis virus. New information on the structural proteins of the Russian tick-borne encephalitis virus, in particular, isoelectric points, was presented in I. V. Krasil'nikov's (Moscow) report.

A large portion of the reports was devoted to influenza virus. S. Ya. Mel'nikov (Moscow) reported on an original immunologic method for isolating influenza virus genes from infected-cell polysomes, making it possible to obtain individual mRNA's for M. proteins and hemagglutinin. The properties of influenza virus virions, the problems of obtaining influenza vaccines and promising diagnostic methods were reported by N. N. Aleksandrov, N. L. Kislitsin, S. A. Zhurnov and I. P. Pestov (Sverdlovsk), M. (Kuntse) et al. (Berlin), V. V. Kupriyanov (Moscow), S. V. Usov (Tomsk) and N. D. Shustov and B. B. Dzantiev (Sverdlovsk). According to G. (Khaidar's) (Berlin) data, influenza virus strains isolated from patients during an epidemic period are highly variable with respect to sensitivity to the action of remantadin in vitro. A possible association of the antiviral action of remantadin, deutiforin and adamantane with disruption of the metabolism of lipid-soluble substances in influenza virus virions and in the cell membrane was pointed out by Yu. M. Sudnik et al. (Minsk).

I. N. Indikov, V. G. Litovchenko (Moscow) and P. Konchek et al. (Bratislava) investigated patterns of interferonogenesis in tissue cultures of diploid human cells and mouse cell hybrids. Yu. B. Umbrashko and I. G. Khofmane (Riga) established a relation between the interferonogenic activity of phage 2 double-stranded RNA and the high molecular weight fraction of the preparation. The possibility of using an indirect variant of the ELISA for the accelerated monitoring and antigenic characterization of interferon was demonstrated by T. I. Kuz'mina (Moscow).

Considerable attention at the conference was given to the development and application of laboratory diagnostic methods for a wide range of infections of viral etiology, as well as the procurement, application and comprehensive evaluation of the reliability of prophylactic preparations. The communications presented examined, in addition to the use of traditional diagnostic methods (A. F. Zalesskikh, Gor'kiy; S. V. Zubov et al., Gor'kiy, G. Nad' and Z. Takachi, Budapest; G. I. Savitskiy, Moscow; A. G. Sergeyev, Sverdlovsk), the possibilities of using immunosorbent methods for indication of arenaviruses (N. S. Apekina, Moscow; A. P. Ivanov et al., Moscow), rotaviruses (I. R. Sarv and V. I. Khaustov, Moscow), hepatitis A virus (T. N. Bystrova, Gor'kiy; N. V. Doroshenko and I. L. Alekseyeva, Moscow; V. Ya. Saulite, Riga) and hepatitis B virus (N. P. Bugayeva, Moscow).

Of particular interest among the reports devoted to the problems of vaccinal prevention was V. Shlikhtova's (Prague) communication devoted to a study of the immunogenicity of a subunit vaccine against herpes simplex virus.

A series of communications examined topics of the isolation, cultivation and monitoring of tissues for vaccine production. M. A. Zaval'nyy and V. M. Kovalenko (Moscow) reported data on features of cell cultivation on microsupports and in various types of cultivators. T. M. Orlova and A. V. Kurbatov (Moscow) presented the characteristics of new lines of diploid and heteroploid cells from green monkey tissues. The obtained tissue cultures proved to be highly sensitive to a broad range of viruses, and one culture (No. 4647) has potential for the preparation of a vaccine against carnivore distemper virus. V. I. Stobetskiy and T. M. Orlova (Moscow) and S. G. Kurumchina and L. V. Averikhina (Sverdlovsk) characterized primary and transplantable cell lines by the frequency of sister chromatid exchanges and karyotypic variability. D. Rozhanski and S. Chernescu (Bucharest) observed an increased frequency of cytogenetic lesions during the chronic infection with cortex virus in vitro compared with the acute infection.

The reports of Yu. S. Boriskin et al. (Moscow) were devoted to the modeling and indication of chronic viral infections in invertebrate and mammalian tissue cultures. V. B. Kurenkov (Moscow) presented data on the variability of strains of the tick-borne encephalitis virus with respect to the DC and C ecological markers. Yu. (Dyurkop's) (Bad Elster) work demonstrated the possible relation between the incidence of enteroviruses in surface drinking water with the population's disease rate. O. E. Lukina (Moscow) developed an effective scheme for sewage purification from enteroviruses using ozonization.

A wide range of methodological techniques and originality in approaches to the study of the pathogenesis of viral infections were demonstrated in the reports of I. S. Vilesova et al. (Moscow), Ya. B. Beikin (Sverdlovsk), N. A. Belyavska (Omsk) and V. V. Bogach (Khabarovsk).

The work of the conference proceeded in an atmosphere of business-like and comradely discussion. The vast majority of reports were carried out at a high theoretical and methodological level. At the concluding session numerous wishes were expressed concerning the benefit of regularly conducting similar conferences in the future.

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CSO: 1840/368

AGRICULTURAL PRODUCTIVITY ENHANCED BY MICROBIAL PRODUCTS

Moscow KRASNAYA ZVEZDA in Russian 3 Jun 82 p 2

[Article by V. Ogarkov, Corresponding Member, USSR Academy of Medical Sciences and Deputy Chief, Main Administration of the Microbiological Industry, USSR Council of Ministers: "Horizons in Bioindustry. Food Program and Science"]

[Text] "...To develop theoretical investigations on topics of genetic engineering in plant, microorganisms and animal breeding and the biotechnology for synthesis of protein and biologically-active substances. To assure creation of new effective means for protecting plants from pests, diseases and weeds and creation of growth regulators and other preparations for agriculture, as well as development and introduction of the technology for industrial production of these substances." Such was one of the tasks presented Soviet science by the May (1982) Plenum of the CPSU Central Committee.

The utilization of microorganisms in agriculture and the prospects for an industry of living cells are discussed by Vsevolod Ivanovich Ogarkov, Deputy Chief, Main Administration of the Microbiological Industry, USSR Council of Ministers, and Corresponding Member, USSR Academy of Medical Sciences. With his presentation we inaugurate a new column "Food Program and Science".

The scientific-technical thought of recent decades has opened truly vast prospects for the use of microorganisms, the unicellular creatures capable of producing fodder proteins, amino acids, vitamins, fats, enzymes and fodder and veterinary antibiotics and protecting plants from diseases and pests. The 23rd CPSU Congress adopted a resolution for the creation in the nation of a new independent branch comprising the microbiological industry. It was assigned the task of providing the national economy, primarily the agriculture industry, with the products of microbiological synthesis. In a short period the young branch increased the total volume of product output, five-fold, including a 20-fold increase for agriculture. Today, if it may be thus expressed, the "agrarian portion" of our output comprises about 80 percent of the microbiological production. Nevertheless, the consumption of protein-vitamin concentrates, amino acids, enzymes, bacterial fertilizers and other

"microbial products" continues to increase, and the further growth and wide utilization of the potential of the microbiological industry has today attained great significance.

Microbiology is among those sciences whose significance for the solution of basic problems in biology and for the development of the national economy is increasing rapidly. The study of microorganisms relates to the solution of the most important practical problems and the broadest theoretical generalizations in genetics, ecology and many other biological trends. Why is this so?

Just recently the word "microbes" usually brought to mind only disease agents. But, as later became clear, these small creatures may not only give rise to disease but may also produce nutrition products, drugs, rare substances, even fuel capable of replacing petroleum. To realize the so impressive potential of microorganisms, to force them to yield the maximum benefit to man is the main task of industrial microbiology.

Successes in the microbiological industry comprise one of the most important processes in the scientific-technical revolution; the development of such areas of the economy as the food industry, health, the chemical and petrochemical industry, metallurgy, and many others, today depends in numerous ways upon these successes. Our scientific developments and their introduction are of special importance for fulfilling the Food Program adopted by the May (1982) Plenum of the CPSU Central Committee.

Since ancient times, bread, wine, beer and cheese have been produced using microorganisms (for example, fermentation yeast); the production of antibiotics and vitamins began fairly recently. But the latest achievements in the area of microbiology are truly impressive. It has been possible, for example, to isolate microorganisms that accumulate protein thousands (!) of times more rapidly than do animals; moreover, the accumulation process can be controlled.

We shall illustrate this with an example. About 0.5 kg protein are produced daily by a cow weighing 500 kg. During the same period, 500 kg yeast synthesize 50,000 kg proteinaceous substances.

The processes of production of fodder microbial protein (protein-vitamin concentrates), developed by Soviet scientists and exploited on a large industrial scale, are capable of speeding the solution of the so-called protein problem.

Acquisition of microorganism protein is distinct from agricultural production: it requires no arable land, does not depend upon climatic and weather conditions, can be precisely planned, yields readily to automation and requires no pesticides.

Laborious scientific investigations have resulted in the isolation of bacteria which when introduced into the soil can fix nitrogen from the air and thus increase the productivity of agricultural plants. The "azotobacterin" and "nitragin" preparations are produced on the basis of such bacteria. The latter, for example, facilitated an increase in soy productivity by approximately 30 percent.

In discussing agriculture one cannot overlook such microorganism applications as the control of agricultural pests, weeds and agents of plant diseases. It has been calculated that these factors remove from world agriculture half of the total possible harvest. A whole series of bacterial, hybrid and viral preparations for the protection of plants, increasing the yields of cereal and vegetable crops, have been developed in the USSR. Bacterial pesticides effectively destroy harmful insects. And, which is particularly valuable, all these preparations possess a strictly selective activity and are absolutely harmless to man and animals. In contrast to chemical preparations, biological preparations do not pollute the environment.

It is known that a large part of the cultivated agricultural crops is used for animal fodder. But are these crops completely utilized here? Is it not possible to reduce their consumption for fattening? In other words, do reserves exist for increasing the intensity of fodder production?

Practice shows that such reserves are available. It has been determined that the primary cause of the overconsumption of fodder is a protein deficit in the diets. Scientists have proven that microorganisms are capable of helping to overcome the protein deficit. Science has provided the technology for the production of fodder yeasts and protein-vitamin concentrates, one tone of which contains fivefold more raw protein and 9- to 11-fold more lysine than does one ton barley. Furthermore, yeasts contain virtually all B group vitamins. One ton protein-vitamin concentrate added to fodder releases 5 to 7 tons grain, enriches 20 tons combined fodder, provides an additional yield of 1.5 tons poultry meat, 30,000 eggs or 0.8 tons pork. At the same time, the cattle fattening period is reduced, resulting in a savings of 10-12 tons combined fodder.

Of special interest is lysine. Without this essential amino acid the synthesis of protein compounds by higher animals is impossible. Large quantities of fodder can be consumed, but if it is deficient in lysine all this will be for naught. Therefore, science is confronted with the task of developing artificial production of the valuable product for its later addition to fodder. Industry has mastered the technology for lysine production. One ton of this product saves no less than 125 tons grain, provides for the additional yield of 10-16 tons pork, 8 tons poultry meat or 250,000 eggs and releases 12-14 tons fish or soy meal (processing wastes).

It can be asserted that complete satisfaction of the agricultural requirement for fodder protein, amino acids and other biologically active supplements will increase the nation's production of animal products by no less than 30 percent, will permit an annual savings of about 100 million tons fodder grain, will produce an additional 19-20 million tons of meat annually (live weight), will sharply increase the production of other types of products and thus yield 26-28 million rubles net income per year.

Several words about other supplements developed in recent years and utilized in experimental production. One thousand tons fodder sugar obtained from wood could replace more than 5,000 tons sugar or up to 20,000 tons fodder beets and release up to 5,000 hectares arable land. One ton fodder yeasts,

according to calculations, replaces eight tons whole milk in rearing young stock. Recommendations have been developed on the addition to combined fodder of artificially-cultivated chlorella, vitamins and enzymes. We shall state that the use of enzymes, in doses not exceeding, in all of 0.02 percent of the total fodder mass, may yield an additional animal weight gain of 10-15 percent, while one percent of the so-called "premixes" may increase the yield of milk by 17 percent with a simultaneous reduction in the expenditure of fodder.

One further important point. The raw material for the microbiological industry is material that we have in some abundance and whose supply does not depend upon the caprices of nature--gas, liquid petroleum paraffins and synthetic alcohols. Large-scale production of fodder protein from petroleum raw material has been organized in the nation.

An additional very important development has taken shape in the field of microbiology. By screening microbial strains--using the achievements of genetic engineering--research will be able to "program" the isolation of bacteria with strictly determined properties. The attention of scientists has also been drawn by the prospects of the microbiological production of products of human nutrition.

Man will strive to supplement agricultural production with microbiological production because such a route is determined by the level of our knowledge and technological development, because it makes possible the production of a higher quality food with fewer expenditures.

Microbiology has vast potential for the further intensification of our agriculture, for increasing soil fertility, the yield of arable land and animal productivity, for the more rational utilization of valuable food products. The methods of biological science are naturally enlisted into the microbiological industry, expanding the range of application of biotechnological processes and confirming the effectiveness of this route.

Further development of the microbiological industry, stipulated by the resolutions of the May (1982) Plenum of the CPSU Central Committee, will permit a large increase in the production for agriculture of the branch's main product types and will facilitate the successful fulfillment of the Food Program.

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HgaI RESTRICTION NUCLEASE-CLEAVABLE OLIGONUCLEOTIDE ADAPTORS: USE IN DNA SYNTHESIS

Moscow BIOORGANICHESKAYA KHIMIYA in Russian Vol 8, No 6, Jun 82
(manuscript received 6 Jan 82) pp 830-839

KOROBKO, V. G., DOBRYNIN, V. N., SEVERTSOVA, I. V., BOLDYREVA, Ye. F.,
BYSTROV, N. S. and KOLOSOV, M. N., Institute of Bioorganic Chemistry imeni
M. M. Shemyakin, USSR Academy of Sciences, Moscow

[Abstract] Description is provided of the synthesis of two types of oligonucleotide adaptors (AI-EcoRI and AI-HindIII, and AII-EcoRI and AII-HindIII) for the cloning of DNA fragments and their subsequent recovery. Both types of adaptors contain a protruding end for joining with a vector, a recognition site for restriction endonuclease HgaI for cleaving off the cloned DNA, and a terminal triplet for the direct selection of recombinant DNA during cloning. A three-stage method was devised for the assembly of synthetic oligonucleotides by the use of the AI adaptors, regardless of whether long or short fragments are desired. The use of AII-HindIII adaptor was exemplified by cloning the dsp (delta sleep inducing peptide) gene in E. coli BMH 71-18 cells, using plasmid pUR51 as the vector. Figures 5; references 20: 3 Russian, 17 Western. [362-12172]

CONSTRUCTION AND PROPERTIES OF VECTOR FOR CLONING PROMOTOR-CONTAINING DNA
FRAGMENTS: CLONING OF E. COLI AND PHAGE T7 PROMOTORS

Moscow BIOORGANICHESKAYA KHIMIYA in Russian Vol 8, No 6, Jun 82
(manuscript received 11 Dec 81) pp 840-846

SERPINSKIY, O. I., KARGINOVA, Ye. A., MIKRYUKOV, N. N. and KRAVCHENKO, V. V.,
All-Union Scientific Research Institute of Molecular Biology, Novosibirsk;
ZAYCHIKOV, Ye. F., MAKSIMOVA, T. G., ONIKIYENKO, A. I. and PLETNEV, A. G.,
Institute of Organic Chemistry, Siberian Branch, USSR Academy of Sciences,
Novosibirsk; and MITINA, Yu. L., Institute of Cytology and Genetics, Siberian
Branch, USSR Academy of Sciences, Novosibirsk

[Abstract] Recombination was used to eliminate the AluI fragment (15 base
pairs) from the DNA of the plasmid pBR322 to create a new vector designated
pSK; the AluI fragment is located in the promotor region of the tet gene
responsible for E. coli resistance to tetracycline (Tc^r). Consequently,
deletion plasmid pSK does not contain the Tc^r phenotype. Cloning of promotor-
containing DNA fragments into pSK DNA at the EcoRI site resulted in recovery
of the Tc^r phenotype if transcription of the fragment coincided with the
orientation of the tet-gene. pSK was also used for the cloning of BspI, Msp,
and AluI DNA fragments, which contain the UV5 promotor of the E. coli lac
operon and the A_2 promotor of bacteriophage T7; in each case the promotor-
containing fragments could be recovered from the recombinant DNA after cleavage
with EcoRI restriction endonuclease. Figures 7; references 23: 6 Russian,
17 Western.
[362-12172]

ENVIRONMENT

UDC: 614.7:632.95

ENVIRONMENTAL HYGIENE AS RELATED TO USE OF CHEMISTRY IN AGRICULTURE

Moscow VESTNIK AKADEMII MEDITSINSKIKH NAUK SSSR in Russian No 11, Nov 81
(manuscript received 5 Nov 80) pp 62-67

[Article by L. I. Medved' and Yu. I. Kundiyeu]

[Text] The importance, complexity and multifaceted nature of problems that are put to environmental hygiene because of the continuous increase in use of chemicals to protect plants and as mineral fertilizers are common knowledge.

Persistent pesticides circulate in the environment continuously and accumulate in different objects, including people. Herein is one of their main hygienic distinctions as xenobiotics.

In order to characterize global pesticide pollution, studies were made of pollutants in preserve zones--Belovezhskaya Forest, several preserves in Transcarpathia, Khersonskaya Oblast and others (Ye. I. Spynu et al., 1980). DDT, its metabolites and hexachlorane were detected everywhere. DDT, its metabolites and hexachlorocyclohexane (HCCH) were found in soil and the grass cover in amounts reaching tenths and thousandths of a milligram per kilogram. It was noted that pesticides penetrate into subsoil water, mainly in amounts of up to hundredths of a mg/kg. These compounds were found in the milk of all tested cows. In inspecting pollution of bodies of water, an increase was found in concentrations of pesticides in ecological chains, in some cases by a factor of 10. Thus, DDT content in reservoir water constituted hundredths-thousandths of mg/kg, in silt up to hundredths and in fish up to tenths of a mg/kg. Thus, even in preserve territories, contamination of the terminal links of ecological chains reaches a level that presents a real hazard to man.

Data on accumulation of pesticides in birds (gulls) and terrestrial vertebrates (axis deer and others) also reflect such a relationship. A study of the dynamics of accumulation of pesticides in different years revealed both an increase in amounts of these agents in a number of animals, and appearance thereof in a large number of species. The findings are indicative of global migration of pesticides in air, subsoil water and fallout with atmospheric precipitation. Several of the organochlorine pesticides are new, constant ecological factors that influence biogeocenoses and man.

We should dwell on yet another aspect of using pesticides, which has been little-studied, that of using them to protect forests. In our country, more than 1 million hectares of forests are treated with pesticides annually. For this reason, a concrete task has been put to hygienists: to work out measures that would prevent the possible adverse sequelae of using pesticides in forests to the health of vacationers. The fact of the matter is that not all of the preventive measures that have already been tried in agriculture can be applied to forestry. It is impossible to solve the above problem without in-depth studies of conditions for using pesticides in forests and disclosure of the patterns of behavior of residual amounts thereof in forest biocenoses.

Studies pursued at the All-Union Institute of Hygiene and Toxicology of Pesticides, Polymers and Plastics, USSR Ministry of Health, revealed that air, wild edible products and water are the principal elements in the forest environment, through which pesticides can reach man; the circulation mechanism is more marked in the forest biocenosis. As compared to agrocenoses, pesticides migrate in smaller amounts beyond the treated territory in the forest. This migration occurs mainly through atmospheric air and water (when there are flowing reservoirs). There is negligible removal of pesticides with superficial drainage and wild edible products in forests. Most of the settled product is fixed on the treated area and, under favorable conditions, can remain there for a longer time than in fields.

Studies (V. A. Zakordonets, 1977, 1978) have shown that the initial concentrations of the most frequently used agents (chlorofos, metathione, carbophos and others) are often close to or in excess of the MPC [maximum permissible concentration] for the air of work zones for 2-3 days. The time of 50% disappearance of these pesticides in forest air is in the range of 1.63-3.51 day. For this reason, the concentrations of most agents drop to MPC levels in atmospheric air within 10-27 days. The initial contamination of forest plants constitutes an average of 2.0-8.0 mg/kg. Half-life for organophosphorus compounds in the forest is 2.26-6.53 days. For this reason, the time required for residual amounts of most of the pesticides in this group to decline to a PRC [permissible residual concentration] is 10-40 days.

Residual amounts of pesticides are detectable in mushrooms and berries on the level of units and tenths of a mg. However, because of migration of residual agents from the top levels of the forest down, for the first 2 weeks it is not uncommon for pesticide levels to be tens of times higher than the PRC in edible forest products.

A "migrational tail" is sometimes observed as a result of intracenotic migration and circulation of pesticides in forests, when residual amounts of pesticide, after dropping to a certain level, remain unchanged for almost an entire year. Thus, in Lithuanian SSR, metathione was detected in forest plants in amounts of 0.08-0.2 mg/kg after 3 months and, after another 9 months, residues thereof constituted 0.01-0.17 mg/kg. It should be borne in mind that the present assortment of pesticides is used against the background of already existing pollution of forests with DDT residues. This pesticide is found in amounts of tenths and hundredths of a mg/kg 5-10 years after it was used, and even in areas that had not been submitted to chemical treatment at all. All this requires that hygienists work out differentiated regulations that would prevent the adverse effects of using pesticides in forests.

Analysis of the results of testing more than 3 million samples in the last 10-12 years at the laboratories of sanitary and epidemiological stations of our country shows that contamination of foodstuffs with pesticides is constantly decreasing. Thus, in the period from 1966-1971 to 1972-1974, the incidence of detecting pesticides in foods has dropped to one-half, while the number of samples with residual amounts thereof in excessive of permissible levels decreased to one-third to one-fourth. The same trend was noted in subsequent years. The incidence of contamination of food by pesticides did not exceed 11.5% in the period from 1972 to 1974, and it dropped to 6.9-7% in 1975-1977. In 1978, only 5.9% of 301,000 samples contained traces of pesticides.

Analysis of overall contamination of foodstuffs by pesticides in different parts of the country revealed that it is even lower in some of them. For example, in Belorussian SSR, pesticides were detected in 0.4-4.5% of the cases in 1972-1974 and 1.2-1.63% in 1976-1978. Low indicators of pesticide contamination of foods are inherent in Lithuanian and Ukrainian SSR. The data of the sanitary and epidemiological service of the Ukraine offer particularly graphic evidence of advances in the area of hygiene of pesticide use. There, detection of pesticides in foodstuffs dropped from 11-13 to 2.98% from 1969 to 1978, while the incidence of traces in amounts exceeding permissible levels dropped from 7.6-8 to 1.2%. There has been drastic reduction of contamination of foods by stable organochlorine pesticides. Thus, the quantity of food samples containing traces of DDT and HCH decreased to almost one-fifth in 1974, as compared to 1961-1965. At the present time, there is a low frequency of detection of DDT and HCH in foodstuffs. DDT is demonstrable in 1.94% of the food samples and HCH in 1.65%. The number of samples with traces in excess of permissible levels constitute 1.28 and 0.54%, respectively (1978). On the whole, there was a decline from 11.2 to 1.5% in detection of organochlorine pesticides (OCP) in foods in the period from 1969 to 1978 (according to data for UkrSSR), while the number of samples with traces exceeding permissible levels decreased from 7.58 to 0.98%.

Information concerning residual pesticides in the biosphere has reached such a volume that it is impossible to submit it to traditional analysis; it is necessary to apply cybernetics to gather, store and specially process data on computers, with consideration of the many factors and complexity of relations in the environment-pesticide system. The applied significance of monitoring pollution of environmental objects by pesticides in different zones of the country and ensuing appropriate preventive measures are combined with the importance of solving a set of scientific and applied problems pertaining to forecasting of an analytical nature. At the present time, testing of a system has been completed, and work has begun on the first phase of putting it in operation.

Numerous studies have demonstrated the link between chemical pollution of the environment and public morbidity level (V. I. Pol'chenko et al., 1975; V. P. Bezuglyy, 1976, 1980; D. P. Kachalay et al., 1979; Ye. N. Sidorenko et al., 1980; L. I. Tkach, 1980, and others). Areas with marked differences in intensity of using the main groups of pesticides (10-fold difference for organochlorine compounds) were selected for field studies. This caused different levels of intake of residual pesticides by man (3-10-fold differences). In

order to prevent possible adverse effects of pesticides on man, it is important to detect pathological changes early, at the stage of reversibility of the process (before development of distinct symptoms of disease), which is the purpose of prenosological diagnostics. Implementation of therapeutic and preventive measures at expressly this stage is the most effective in preventing progression and transformation of the process into clinically defined forms of pathology. To perform this task, it is imperative to conduct mass scale screening of essentially healthy individuals. However, proper attention has not yet been given to this important matter. When medical examinations are performed, attention is focused on examining people with already formed pathology, while its origin and onset remain outside the physician's field of vision.

The studies being conducted in this direction at the clinics of the All-Union Institute of Hygiene and Toxicology of Pesticides, Polymers and Plastics, USSR Ministry of Health, Kiev Institute of Industrial Hygiene and Occupational Diseases and others have made it possible to work out methodological approaches to investigation of prepathological states, to describe the essence thereof, to recommend a number of therapeutic and preventive measures to prevent their progressive course (L. M. Kaskevich et al., 1977; Ye. P. Krasnyuk, 1974; L. M. Kaskevich, 1980). In particular, studies of immunological reactivity of the body revealed depression of natural resistance factors in 50% of the essentially healthy people who work with pesticides. The earliest indication was a decrease in level of normal antibodies--heterophil agglutinins. A decrease in serum immunoglobulins was also demonstrated, mainly of the G type, which are a principle class of immunoglobulins that include most of the protective antibodies. In a region where organochlorine pesticides are used intensively, a decline of heterophilic agglutinin level (0.94 ± 0.11 arbitrary units) was found in healthy people as well, whose profession did not require contact with pesticides, and in a region with limited use thereof the levels of heterophil agglutinins in healthy residents were considerably higher (3.82 ± 0.14 arbitrary units). Depression of immunological reactivity was combined with a decrease in ascorbic acid, which is consistent with well-known data to the effect that vitamin C deficiency alters significantly the immunobiological reactivity of the body, its resistance to various deleterious factors. Testing of lipid metabolism in healthy residents of the region (all age groups examined, including 21 to 30 years) of intensive use of organochlorine pesticides revealed considerable elevation of free cholesterol level in blood serum. A decline of the coefficient of cholesterol firmly bound with protein was also noted. In view of the results of studies of the vascular system of people whose profession involves contact with pesticides (increased tonus of cerebral vessels at an earlier age than in the control group, faster aging evolution of vessels), pesticides should be considered a risk factor with regard to vascular pathology, primarily atherosclerosis. It should be stressed that at this stage of their development, these changes are reversible. Thus, according to the results of a 3-4-year follow-up, no more than 25-30% of the subjects presented a progressive process. An age-related study of the respiratory system revealed earlier (than in the control group) decrease in functional capabilities of the bronchopulmonary system (I. Ye. Kolpakov, 1979). In some occupational groups (for example, beet growers), metabolic disturbances were found (diminished functional capability of the glutathione-ascorbic acid system, which is an important compensatory system of the body).

Individuals with the above-mentioned functional disturbances are more vulnerable to additional deleterious factors (stress situations, bacterial infection, unwise work and rest schedule, etc.). The obtained data explain the rise, which was found by many authors, in incidence of cardiovascular, respiratory and other diseases in regions where pesticides are used intensively and in groups whose occupation involves contact with chemicals. Prenosological detection helps pick up people out of essentially healthy groups, who present a higher risk of development of clinically circumscribed forms of pathology, and this is of first and foremost importance to prevention thereof.

When elaborating the strategy for scientific forecasting and prevention of undesirable genetic consequences of intensive use of chemistry in agriculture, the guiding principle should be the one adopted in the Soviet Union: to make wise use of natural resources, according to which one should not raise the question of preventing all factors, but of properly assessing the permissibility of any intervention. When guided by this principle, we can distinguish two main tasks in the genetic aspect of environmental hygiene. The first consists of identifying environmental pollutants--mutagens; determining their genetic activity; developing genetic standards and regulations with consideration of the degree of potential mutagenic hazard of agents. The second task is to set standards for overall levels of mutagens in the environment, with consideration of the combined and complex effects of different mutagenic factors. As we know, pesticides make up a large group of agents that are referable to different classes of chemical compounds. Among them, we can find quite a few analogues of drugs and agents used in different sectors of industry or which are industrial by-products. This warrants the belief that the knowhow gained in studies of mutagenicity of pesticides and the developed approaches to assessment of their mutagenic hazard could be well-used in the study and evaluation of mutagenicity of many compounds used for other purposes. At present work has been virtually completed on identifying mutagen pesticides, including a record, generalization and analysis of data on mutagenicity of pesticides (A. I. Kurinnyy and M. A. Pilinskaya, 1976). A large volume of research has been conducted on mutagenic activity of pesticides that are used widely in our country; the first methodological recommendations have been worked out and published that deal with assessment of potential mutagenic hazard of pesticides (M. A. Pilinskaya and A. I. Kurinnyy, 1980).

Studies have confirmed the hypothesis that pesticides as a whole are referable to low-intensity environmental mutagenic factors. In spite of the fact that, of the total number of agents studied, 41.4% induced a mutagenic effect, only 3 of them were classified as agents with a high degree of potential mutagenic hazard. For this reason, it is now time to raise the question of granting permission to use new pesticides in the event they have marked mutagenic properties and to replace mutagenic pesticides that are already in use with products that are genetically safe. At the present time, studies of mutagenicity of pesticides are being pursued in accordance with a unified plan, and the findings are submitted to the Committee for the Study and Regulation of Use of Toxic Chemicals under the USSR Ministry of Health, after a review of the obtained data by a consultant group that assesses the mutagenic hazard of pesticides, which is part of the Section of the State Committee of the USSR for Science and Technology. This is instrumental in improving the quality of research and assures great objectivity of conclusions. Unquestionably,

restrictions on the use of some pesticides and recall of the most hazardous ones will reduce the genetic risk. However, studies of levels of chromosome aberrations in residents of areas notable for intensive use of pesticides revealed that the problem of preventing the genetic consequences of using chemicals will be solved only if standards are set for overall mutagen levels in the environment.

Intensive use of chemistry in agriculture could lead to poisoning among people engaged in manual agricultural work. Such cases are observed, in particular, when using manual labor to care for sugar beet fields. As we know, a distinctive feature of raising sugar beets is that large amounts of organic and mineral fertilizers are applied, and intensive use is made of pesticides. New chemical compounds could be formed in the deep layers of the soil, as a result of chemical reactions and biochemical processes involving soil microflora. As shown by the results of analyses, these compounds include some that are highly toxic, much more than pesticides (Yu. I. Kundiyeu et al., 1975, and others). In particular, carbonyl, cyanide and phosphorus-containing compounds, as well as ammonia, hydrogen chloride and others have been discovered. When the soil is loosened manually when temperature rises drastically, the above agents migrate intensively into the breathing zone of workers. Prevention of this type of poisoning requires research on the borderline of hygiene, toxicology and agrochemistry. The results of our studies warrant recommending the safest mixtures of pesticides, time and conditions of using them with consideration of use of mineral fertilizers. However, radical prevention of such poisoning is possible only if there is a complete changeover to industrial technology of agriculture.

The problem of hygiene of using pesticides has grown more complex in the last decade: first-generation pesticides (highly toxic and persistent agents) were replaced with the second generation, some agents in which have a greater capacity for eliciting long-term effects. Now we are already dealing with the third generation of pesticides. These are basically new organophosphorus compounds with selective action, which contain peptide bonds along with carboxyester groups. Among them, agents containing amino acid residue are of special interest. The products of degradation of such compounds are referable to biogenous agents that will not pollute the environment. We should include among third-generation pesticides the synthetic pyrethroids. Apparently, we can expect a return to use of some of the highly toxic organophosphorus compounds, but in granulated form. In this form they will be less detrimental to the health of workers and the environment than many agents with low toxicity, which have greater persistence and, moreover, are capable of eliciting long-term effects. In our country, it is planned to create a special sector of small-volume chemical industry, with mobile technology for accelerated production of new pesticides. This, in turn, will require refinement of hygienic and toxicological research, in-depth investigation of the health status of people and improvement in the area of setting hygienic standards for pesticides in the environment.

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10,657

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CHEMICAL COMPOSITION OF BOTTOM DEPOSITS AND MIGRATING FORMS OF
TRACE ELEMENTS THEY CONTAIN

Moscow GIGIYENA I SANITARIYA in Russian No 4, Apr 82 (manuscript received
20 Jul 81) pp 76-78

[Article by T. L. Radovskaya, L. A. Khazemova, N. P. Makarenko and L. V.
Vinogradova, Sverdlovsk Scientific Research Institute of Industrial Hygiene
and Occupational Diseases]

[Text] Regardless of the analytical method used, a differentiated approach must be used for stripping samples for quantitative assays of a wide range of elements in bottom deposits [sludge?]. Different results could be obtained, depending on the method of treating samples. It is impossible to assay fluorine and silicon in the acids indicated. Consequently, to assay different elements we need different methods of transforming specimens to a soluble state. For this reason, a scheme was developed for stripping ["opening"?] bottom deposits, which shows that it is expedient to analyze arsenic, lead, cadmium and chromium in the same specimen after treating it with aqua regia, whereas for copper, iron, zinc, chromium, manganese, nickel, cobalt, molybdenum and calcium, where use of the same batch is also desirable, silicon must first be removed with hydrofluoric and sulfuric acids, and then the samples dissolved using nitric, perchloric and hydrochloric acids. Silicon should be assayed in a separate batch of bottom deposit, after melting with sodium peroxide, and fluorine from another batch using pyrohydrolysis to isolate it.

Since there is no standard sample of bottom deposit, we analyzed a standard soil sample using the proposed scheme. The obtained data were indicative of satisfactory reliability of assays of some elements and, consequently, validity of the proposed analytical scheme.

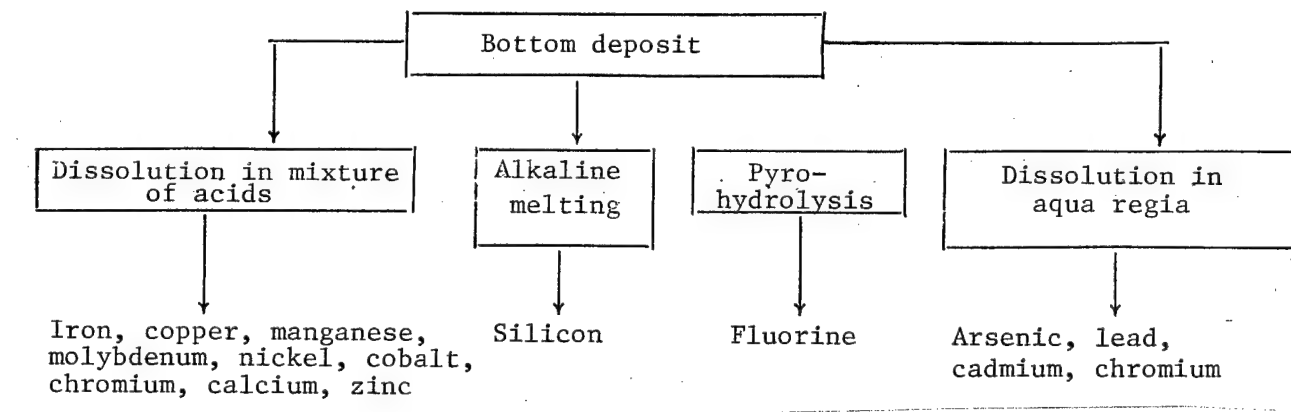
To investigate the possibility of migration of trace elements from bottom deposits, we examined aqueous, hydrochloric (pH 4.5) and ammonium acetate (pH 6.8) extracts obtained by a standardized method, with 1:10 proportion of solid and liquid phases and shaking the specimens for 1 h (K. V. Verigina and Yu. I. Dobritskaya). The liquid phase of the specimen was filtered and analyzed. We used electrochemical, photometric and trilonometric analytical methods.

Preparation of samples: The sample of bottom deposit was centrifuged at 5000 r/min for 10 min for separation of interstitial water and dried at room

temperature to an air-dry state. The dry sample is ground thoroughly in an agate mortar and passed through a 100-mesh sieve.

Dissolution in aqua regia: 0.5 g of prepared sample is put in a 50-ml beaker, 2 ml aqua regia is added, a watch glass lid is applied, and it is left to stand for 1 day. The contents of the beaker are stirred periodically. We add 10 ml water, mix the dissolved sample thoroughly and pass it through a "blue ribbon" filter into a 25-ml measuring flask. The sediment on the filter is washed, volume of solution is brought up to the mark and mixed. A blank test ["dry run"] is run concurrently.

Scheme for stripping sample of bottom deposit for analysis



To assay lead and cadmium, an aliquot of the obtained solution is treated with perchloric acid, evaporated to salts, 10 ml phosphate-perchlorate background added (0.9 m phosphorus and 0.5 m chlorine) and polarographed on a PPT-1 in alternating current mode with peak potential of 0.78 V for lead and 0.9 V for cadmium.

To assay arsenic, an aliquot of solution is treated with sulfuric acid, evaporated to vapor, the walls of the beaker are washed with water and the procedure is repeated. We then add 40 ml 20% sulfuric acid and the solution is heated to the boiling point. The cooled sample is quantitatively transferred into an instrument for assaying arsenic according to Gutzeit (GOST 2874-73).

Dissolution in mixture of acids: A 1-g batch of air-dried sample is placed in a platinum dish, 10 ml hydrofluoric acid and 1.5 ml sulfuric acid are added, 1:1, and evaporated with sulfuric acid on a hotplate to remove silicon. The treatment with hydrofluoric acid is repeated twice. Then 10 ml nitric acid is added, the contents of the platinum dish are heated to boiling, cooled and the sample is quantitatively transferred to a heat-proof 100-ml beaker, rinsing the dish with water. The solution is evaporated to a volume of 20 ml, then 5 ml perchloric acid is added and it is evaporated until dry. We then add 5 ml hydrochloric acid and again evaporate the sample until it is dry. It is cooled, 15 ml hydrochloric acid is added, then heated until the sediment dissolves, 15 ml water is added, the beaker is covered with watch glass and

brought to a boil. The solution is cooled and filtered through a "blue ribbon" filter into a 50-ml measuring flask. The filter is washed in water and volume brought up to the mark. The solution is thoroughly mixed. A blank test is run concurrently in the course of analysis. Aliquots are prepared for photometric assay of iron with orthophenanthroline, chromium with diphenyl carbaside, cobalt with nitroso-P salt, manganese with our stain, nickel with dimethyl glyoxime (Z. Marchenko), zinc with rhodamine C (Yu. Yu. Lur'ye and A. I. Rybnikova), molybdenum with zinc dithiol (T. V. Agranovich and N. V. Stashkova), copper using the disulfide reaction (T. L. Radovskaya et al., 1979) and calcium by the trilonometric method (M. M. Sochevanova).

Assay of fluorine: 0.05 g air-dried sample is placed in a quartz tray, 1 ml 5% settled calcium oxide solution is added for "fixing" of fluoride ion and evaporated at 80°C until dry. The sample is then submitted to pyrohydrolysis and fluorine is assayed by the photometric method using a zirconium-eriochromocyanin reagent (L. A. Khazemova et al.).

Assay of silicon: 0.1 g sample is placed in an iron crucible, 2 g sodium peroxide is added and the contents mixed thoroughly. It is melted at 600-700°C for 5 min. Before leaching out the sample, the scale [sinter] is removed from the outer surface of the crucible. The crucible is then placed horizontally in a polyethylene 200 ml beaker, 75 ml hot water is carefully added and a polyethylene lid applied. After termination of the intensive reaction, the crucible is removed with a polyethylene rod and washed in water. Immediately, 15 ml hydrochloric acid is added, the solution is stirred and transferred together with the scale into a 500-ml measuring flask. Hot water is added to the narrow part of the flask and the contents shaken. The solution is allowed to cool gradually to room temperature, water added to the mark, thoroughly mixed and aliquoted for assaying silicon (T. L. Radovskaya et al., 1972).

Analysis of interstitial water, aqueous and hydrochloric extracts presents no difficulties. The specific feature of analysis of acetate extracts for all elements, with the exception of zinc and fluorine, is that there is preliminary breakdown of acetate salts by means of repeated treatment of the solution with nitric acid, followed by decomposition of the sample with reagents recommended in the relevant methods of analysis. One can assay zinc in an acetate extract using rhodamine C directly, submitting the sample to photometry in relation to a sample of acetate solution put through a "dry run" of analysis. Fluorine is assayed with a fluorine-selective electrode, and the calibration scale is plotted against the background of the acetate solution used, pH 6.8.

We analyzed bottom deposits collected from different depths following this scheme of analysis. The results indicate that there is accumulation of pollutants in the top layer of bottom deposits due to sewage dumping.

As a result of analysis of extracts from bottom deposits, it was determined that the extent of extraction of elements increases with increase in their concentration in the initial samples, and in an aqueous extract, there can be an increase in, for example, arsenic and zinc content by an average of a factor of 10^1 , as compared to interstitial water, and by a factor of 10^2 in hydrochloric extract. As for the acetate extract, due to the process of complex formation, there is up to 10^3 increase in zinc and cadmium extraction.

Conclusions

1. A scheme was developed for analysis of bottom deposits, which is based on differentiated dissociation of samples into several components.
2. It is expedient to use the proposed scheme to examine the chemical composition of bottom deposits, regardless of the methods used to analyse elements in question (photometric, electrochemical, atom absorption).
3. Analysis of different extracts from bottom deposits shows that there are migrating forms of toxic elements which could pass into the liquid phase under appropriate conditions.
4. The proposed scheme for analysis of bottom deposits and different extracts from them can be recommended for the study of chemical composition and demonstration of migrating forms of elements in order to make sanitary and hygienic forecasts of water quality.

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10,657

CSO: 1840/332

EPIDEMIOLOGY

UDC 616.61-002.151-053.2

HEMORRHAGIC FEVER OUTBREAK WITH RENAL SYNDROME

Kazan' KAZANSKIY MEDITSINSKIY ZHURNAL in Russian Vol 63, No 2, Mar-Apr 82
(manuscript received 26 Mar 81) pp 3-5

AMINOV, D. G., VISHEV, A. I. and AKHMEDOV, M. G., Chair of Epidemiology,
Bashkir Medical Institute imeni 25th Anniversary of the Komsomol, Municipal
Sanitary Epidemiologic Station, Ufa

[Abstract] Hemorrhagic fever outbreak with renal syndrome was diagnosed at an Ufa Pioneer summer camp in July-August 1975, which involved 49 children and 14 adults. The primary reason for the outbreak was inadequate rodent control at the camp and in the surrounding forest. The delay in proper rodent eradication measures and misdiagnosis of some of the early cases led to the appearance of new cases throughout August. References 8 (Russian). [375-12172]

UDC 616.831-002-022:578.833.26]-036.2(47+57)

EPIDEMIC MANIFESTATIONS OF NATURAL FOCI OF TICK-BORNE ENCEPHALITIS AND ITS PREVENTION IN USSR

Moscow MEDITSINSKAYA PARAZITOLOGIYA I PARAZITARNYYE BOLEZNI in Russian
Vol 60, No 3, May-Jun 82 (manuscript received 24 Nov 81) pp 3-7

IVANOVA, L. M., Main Sanitary-Epidemiologic Administration, RSFSR Ministry of Health, Moscow

[Abstract] A review is presented of the epidemiologic history of tick-borne encephalitis (TBE) in the USSR, which showed that morbidity varied from 0.5 to 2 per 100,000 inhabitants during 1965-1970, and thereafter between 0.5 and 1. The highest incidence of TBE continues to be in the rural economic region (2.7-6.5 per 100,000 inhabitants during 1970-1980); such patients account for 32-49% of the total number of patients in the RSFSR. In the Western and Eastern Siberian economic regions the incidence increased from 2 to 4 and from 0.5 to 2.5 during that period of time, respectively. While TBE appears to be under control in the European part of the USSR (RSFSR, Ukraine,

Belorussia), the morbidity figures for the Soviet Far East can be expected to rise in light of the economic development of that area. Measures for tick control will have to be strengthened, including massive spraying of forests with DDR, and emphasis placed on the development of effective vaccines and the use of immune gamma-globulin for prophylaxis and treatment. Figures 2. [354-12172]

UDC 616.831-002-022:578.833,26]-036.2(57.61/.64)

PROBABILITY OF INFECTION WITH TICK-BORNE ENCEPHALITIS IN LESSER KHINGAN MOUNTAINS AND NORTHERN AMUR REGION

Moscow MEDITSINSKAYA PARAZITOLOGIYA I PARAZITARNYYE BOLEZNI in Russian Vol 60, No 3, May-Jun 82 (manuscript received 29 Apr 81) pp 10-13

VERETA, L. A., YUZHAKOV, L. I., OSTROVSKAYA, O. V., NIKOLAYEVA, S. P., VOLKOV, V. I., DOLGIKH, A. M., SHCHUKIN, A. V., MURATOV, I. V., MZHEL'SKAYA, T. V. and DOVGALEV, A. S., Scientific Research Institute of Epidemiology and Microbiology, Khabarovsk

[Abstract] Previously described index of probability was employed in evaluating the risk of infection with tick-borne encephalitis (TBE) for several occupational classes (geologists, beekeepers, forestry workers, etc.) in the Lesser Khingan Mountains and in the northern Amur region. The study, conducted in 1971-1974 and 1978-1980 involved determination of the population density of the tick *Ixodes persulcatus* and its infectivity with the TBE virus, as well as passive hemagglutination serology and questionnaire responses. The results showed that the index of probability of TBE in the endemic territories varied from year to year (0.01-0.44) and was highly correlated with tick infectivity ($r = +0.93$) and moderately related to tick density ($r = +0.4$). These findings indicate that the index of probability can be used in planning prophylactic measures. References 10 (Russian). [354-12172]

REPRODUCTION OF POWASSAN AND WEST NILE VIRUSES IN MOSQUITO Aedes Aegypti IN VIVO AND IN VITRO IN CELL CULTURE OF THE VIRUSES

Moscow MEDITSINSKAYA PARAZITOLOGIYA I PARAZITARNYYE BOLEZNI in Russian
Vol 60, No 3, May-Jun 82 (manuscript received 23 Mar 81) pp 13-15

KISLENKO, G. S., CHUNIKHIN, S. P., RASNITSYN, S. P., KURENKOV, V. B. and
IZOTOV, V. K., Institute of Poliomyelitis and Viral Encephalitides, USSR
Academy of Medical Sciences; Institute of Medical Parasitology and Tropical
Medicine imeni Ye. I. Martsinovskiy, USSR Ministry of Health, Moscow

[Abstract] Studies were conducted on the reproduction of the Powassan and West Nile viruses in Aedes aegypti and in cell culture. The results showed that the Powassan virus failed to replicate both in vivo and in the cell culture since in both cases viral titers fell from the time of infection until complete disappearance on the 14th day. However, West Nile virus reproduced under both conditions as indicated by steady titers for the 14 day period of observation. Figures 1; references 26: 6 Western, 20 Russian.
[354-12172]

INFECTIVITY OF FARMSTEAD POPULATIONS OF TICK ORNITHODORUS PAPILLIPES BIR. WITH AGENT OF TICK-BORNE RELAPSING FEVER IN UZBEKISTAN

Moscow MEDITSINSKAYA PARAZITOLOGIYA I PARAZITARNYYE BOLEZNI in Russian
Vol 60, No 3, May-Jun 82 (manuscript received 16 Apr 81) pp 23-28

YERSHOVA, A. S. and VASIL'YEVA, I. S., Institute of Medical Parasitology and Tropical Medicine imeni Ye. I. Martsinovskiy, USSR Ministry of Health, Moscow

[Abstract] Studies conducted in 1977-1979 in the Namagan and Andizhan Oblasts of Uzbekistan monitored the population density of the soft tick Ornithodorus papillipes Bir. and the rate of infectivity with the relapsing fever agent at various farmsteads. In both oblasts the agents causing spirochetemia in guinea pigs were determined to be identical. The resultant data showed that in both oblasts the infected specimens were essentially identical (1.2-1.7%). Therefore, the risk of human infections in both regions is comparably high. Figures 1: references 28: 2 Western, 26 Russian.
[354-12172]

DIRECT COUNTING METHOD FOR BORRELIA AND OTHER BLOOD PARASITES

Moscow MEDITSINAKAYA PARAZITOLOGIYA I PARAZITARNYYE BOLEZNI in Russian
Vol 60, No 3, May-Jun 82 (manuscript received 8 Oct 81) pp 28-31

KRYUCHECHNIKOV, V. N. and SHCHERBAKOV, S. V., Scientific Research Institute
of Epidemiology and Microbiology imeni N. F. Gamaleya, USSR Academy of
Medical Sciences, Moscow

[Abstract] The method devised by Magnuson et al. (Am. J. Syph., 32, 1-18, 1948) has been modified to obtain blood counts of Borrelia and other blood parasites. The essential features involved placing a small sample of blood or other body fluid on a microscope slide, covering it with a cover glass, and counting under low power, using an ocular with an appropriate grid for comparison with standard suspensions. Figures 3; references 3: 1 Russian, 2 Western.

[354-12172]

EXPERIMENTAL TRANSMISSION OF VISCERAL LEISHMANIASIS TO GOLDEN HAMSTER BY
SANDFLIES PHLEBOTOMUS LONGIDUCTUS PARR. 1928 AND PH. SMIRNOVI PERF. 1941

Moscow MEDITSINSKAYA PARAZITOLOGIYA I PARAZITARNYYE BOLEZNI in Russian
Vol 60, No 3, May-Jun 82 (manuscript received 12 May 81) pp 49-53

STRELKOVA, M. V., DERGACHEVA, T. I., ALEKSEYEV, A. N. and PASSOVA, O. M.,
Institute of Medical Parasitology and Tropical Medicine imeni
Ye. I. Martsinovskiy, USSR Ministry of Health, Moscow

[Abstract] Experimental studies were conducted to determine whether Phlebotomus longiductus and Ph. smirnovi could serve as vectors of L. donovani, as has been demonstrated for other Phlebotomus sp. The results showed that both species could be infected on forced-feeding with L. donovani promastigotes or as a result of feeding on golden hamsters at depilated sites injected intracutaneously with mastigotes. L. donovani developed in gastrointestinal tract of the sandflies at 24° C during one gonadotrophic cycle (8-11 days), and were transmitted by the sandflies to healthy hamsters when allowed to feed on them. Both species were also shown to attack man, dog, Caspian gecko, and the gerbil. References 29: 13 Western, 16 Russian.

[354-12172]

UDC 616.98:579.843.95]-036.2:911.3(575)

HYDROGEOLOGIC INDICATORS IN IDENTIFICATION OF STABLE ENZOOTIC PLAGUE FOCI

Moscow MEDITSINSKAYA PARAZITOLOGIYA I PARAZITARNYYE BOLEZNI in Russian
Vol 60, No 3, May-Jun 82 (manuscript received 23 Feb 81) pp 80-83

SERZHANOV, O. S., AUBAKIROV, S. A., AGEYEV, V. S., MATAKOV, M. I. and
CHERVYAKOV, V. D., Central Asian Scientific Research Antiplague Institute,
USSR Ministry of Health, Alma-Ata

[Abstract] Evaluation of the hydrogeologic factors favoring stable enzootic plague foci in the Central Asian deserts led to the identification of areas with lentils and lenticles of fresh water as a key factor. In such areas gerbil burrows retain relatively high humidity and low temperatures which favor high flea populations and persistence of an active rodent-flea infectious cycle. Figures 2; references 20 (Russian).
[354-12172]

UDC 576.858.75.095.1:576.6

PERSISTENCE OF GENES OF EPIDEMIC VIRUSES IN NATURAL INFLUENZA A POPULATIONS

Moscow USPEKHI SOVREMENNOY BIOLOGII in Russian Vol 93, No 3, May-Jun 82
pp 323-337

L'VOV, D. K. and ZHDANOV, V. M., Institute of Virology imeni D. I. Ivanovskiy,
Moscow

[Abstract] A review of virologic and serologic studies on animal and human populations, as well as the application of molecular genetics techniques to influenza A viruses, has shown that the latter consist of an extremely heterogenous population. The influenza A virus can be regarded as a species possessing a common genome which, as a result of mutations and recombinational events, can give rise to new genetic entities favoring the survival of influenza A virus in nature. References 108: 1 Czech, 33 Russian, 74 Western.
[355-12172]

GENETICS

UDC: 616-055:5/.7:006"1981-1985"

DEVELOPMENT OF MEDICAL GENETICS UNDER 11TH FIVE-YEAR PLAN AND INTRODUCTION OF ITS ADVANCES TO PRACTICE

Moscow VESTNIK AKADEMII MEDITSINSKIKH NAUK SSSR in Russian No 6, Jun 82
(manuscript received 16 Dec 81) pp 3-8

[Article by N. P. Bochkov, Institute of Medical Genetics, USSR Academy of Medical Sciences, Moscow]

[Text] In the light of the decisions of the 26th CPSU Congress concerning development of medical science and public health, geneticists must solve problems of identifying the mechanism of genetic processes in vital functions of the organism, upgrade preventive, diagnostic and therapeutic methods for hereditary diseases. The question of primary prevention of diseases is in first place in all scientific and practical work dealing with safeguarding the health of the public. We should consider, from this point of view, the plans for development of medical genetics under the 11th Five-Year Plan.

It is a known fact that basic leaps in development of medicine were related to general biological discoveries (cell theory, microbiology, phagocytosis, physiology of the nervous system, etc.). At the present time, fruitful use is being made of genetic conceptions for progress of medicine. One could call human genetics the modern philosophy of medicine. Its advances in recent years have made it possible to connect many chains of scattered events referable to onset and course of pathological processes. The basis for this fundamental influence of genetics on medicine was primarily the development of general human genetics. Detailed listing of structure and function of genetic units began to advance with particular speed because of development of new methods, which made it possible to turn from the organismic and tissular levels of evaluating the discreteness of genetic signs to the cellular and molecular levels. We can now speak of anatomy and physiology of the genome. At the present time, assessment is being made of genetic determination of cellular receptors, enzymopathies, primary products of genes and even RNA transcripts. This is not a simple reduction of discreteness of a feature, but approximation to its primary determination. And the fewer the intermediate steps, the more accurate the genetic evaluation.

To illustrate current characterization of the genome, we can cite data on the dynamics of detection of genetic traits in man: 412 in 1958, 1487 in 1966, 1545 in 1968, 1876 in 1971, 2336 in 1975, 2811 in 1978 and 3217 in 1981. The

increase in number of genes localized in specific chromosomes and, occasionally, even in loci, is growing at the same increasing pace: 4 of them were discovered prior to 1968, 219 in 1973, 247 in 1974, 300 in 1975, 374 in 1977, 443 in 1979 and 496 in 1981.

The speed of progress in modern science is definitiely attributable to collaboration of scientists and exchange of information. Without having scientists join forces human genetics would not have such fundamental generalizations and discoveries as it has had in the last 10 years, such as establishment of all groups of linkage and localization of almost 20% of the genes, identification of primary products of mutant genes, proof of genetic heterogeneity of hereditary diseases, development of methods of prenatal detection of hereditary diseases, demonstration of chromosomal polymorphism in human populations, synthesis of human genes, determination of the routes of evolution of karyotypes of primates, or more precisely of hominids. We could add to this the generalization of numerous data on diseases with chromosomal instability, mutation process and multifactorial diseases.

A wide range of theoretical and applied problems is represented in the plans for development of medical genetics under the 11th Five-Year Plan. The most important ones are included in the State program, whose purpose is "to investigate genetic and molecular mechanisms of immunity disturbances and hereditary diseases, and to develop on this basis the ways and means of prevention, diagnosis and treatment thereof."

In the last 5 years, serious attention was devoted in our country, as well as all over the world, to molecular-biological and molecular-genetic studies of hereditary diseases. It became possible to study them on these levels thanks to the advances in physicochemical biology, particularly gene engineering. Of basic importance here was the fact that, by studying expression of human genes on different levels it is possible to adopt a new approach to the problem of clinical polymorphism and genetic heterogeneity of hereditary diseases. The appropriate methodology does not yet exist for all genes, but geneticists of the USSR are already working with globin, collagen and ceruloplasmin genes, mutations of which elicit such serious diseases as hemoglobinopathy, connective tissue diseases and hepatolenticular degeneration. Genes are being synthesized by the enzymatic method; recombinant DNA are being produced with synthetic genes; their structure is being studied by means of restriction mapping. It is apparent from this set of methods that the assault on human genes has begun in earnest. Expressly this is leading to profound knowledge about pathology. For example, before molecular and genetic research, simply α - and β -thalassemia were known. At present, there are four known forms of α -thalassemia and nine of β -thalassemia, with exact descriptions of molecular changes.

Molecular biological conceptions turned out to be fruitful for analysis of individual predisposition for diseases. Particularly interesting studies of this kind are being conducted in our country with regard to mental and endocrine diseases. Work dealing with a search for biological markers of predisposition will be continued under the 11th Five-Year Plan. A new molecular biological chapter of genetics and pathology--cellular receptors--merits special attention. The study thereof will clarify many previously unclear questions of pathology, particularly tolerance for certain compounds and hormones.

Biochemical genetic investigations are a sort of continuation of molecular genetic studies. Under the 11th Five-Year Plan, they will be directed toward investigation of activity and physicochemical properties of enzymes in the presence of metabolic hereditary diseases (lysosome, amino acid and carbohydrate metabolism). There is strong genetic heterogeneity in these groups. Biochemical genetic understanding (particularly knowledge about pathological metabolites) of these serious forms of hereditary diseases will help upgrade methods of early (or prenatal) diagnosis, evaluation of their incidence and plotting geographic maps of their distribution.

The methods of cellular genetics opened up vast opportunities. Advances in mapping genes and identification of the biochemical routes of expression of mutations are linked with them. Without a doubt, methods of cellular genetics are promising for in-depth analysis of the pathogenesis of hereditary diseases as related to diverse phenotypic manifestations of mutant genes on the cellular level. A real possibility is already appearing to record primary cellular disturbances that hold a key place in the pathogenesis of hereditary diseases. There are different ways of expression of a pathological process in cells in the presence of different diseases. Of the numerous structural and functional distinctions of cells in the presence of hereditary diseases, the following questions were singled out to be studied under the 11th Five-Year Plan: proliferative and clone-forming capacity of cells from patients with hereditary diseases; manifestation of differentiated functions (for example, collagen synthesis) in cells with chromosome and genome mutations; genetic control of formation and function of cellular receptors. A bank of human cell lines with monogene and chromosome diseases will be established to solve these problems. The foundation for such a bank was laid under the last five-year plan. A collection of cells was gathered from more than 150 individuals with hereditary diseases. The cell line bank is a sort of depository for standards, which can always be used to diagnose diseases in specific families by means of comparison, as well as for further investigation as progress is made with regard to methods.

Under the 11th Five-Year Plan, cytogenetic research is based on the major advances made in the last 10 years in connection with discovery of methods for differential staining and implementation of the 5-year interinstitute program for the study of chromosome polymorphism. In the theoretical aspect, efforts will be concentrated in the next few years on structural and functional characterization of different chromosome regions, ultrastructure and correlation between macromolecular components. First of all, there will be development of methods of determining the structural and functional state of regions containing ribosomal genes. Then these regions will be studied in normal individuals and those with chromosome aberrations. Modern investigation of human chromosomes requires development of ultrastructural methods that would permit identification of structural, chemical and replication characteristics on the basis of length of chromosomes. It will then be very important to compare these characteristics when there is a normal and altered set of chromosomes. The prerequisites are already available for such fine cytogenetic studies. For example, the available methods make it possible to study interaction of histones and nonhistone proteins with DNA in individual chromosomes, and rate of replication.

In addition to molecular cytogenetic studies, there will also be continuation of traditional research on structural variants of human chromosomes and their

pathological effects. The main objective of this applied work is to improve differential diagnostics of congenital developmental abnormalities in man, since they are attributable to chromosome disturbances in most cases. By the end of this 5-year period, methodological recommendations must have been prepared for identification and keeping records of structural variants of chromosomes. For this purpose, quantitative methods will be developed for estimating the size of variable heterochromatin regions of human chromosomes (most attention is being given to them), their variability will have been described in normal individuals and the significance determined to development of undifferentiated oligophrenia, miscarriages and multiple developmental defects.

In addition to laboratory studies on the molecular genetic, cytogenetic and cellular levels, theoretical research on medical genetics is being pursued in clinical practice as well. We refer to investigation of expression of genetic information on the systemic level. The main issue here is referable to causes of clinical and genetic heterogeneity of hereditary pathology, namely: to what extent is it determined by the nature of mutations, genotype of the individual or environmental conditions. The causes of clinical polymorphism will be studied by means of interfamily and intrafamily comparisons of the same forms, in order to answer the following question: Must a nosological form be "disconnected" into several forms or should different forms be "connected" into a single form? The program for the current five-year plan provides for unified surveys of patients by clinical and laboratory methods, which will make it possible to integrate the data of different researchers and make faster identification of the causes of polymorphism of concrete nosological forms. Registers of hereditary pathology may be very helpful in this work. There are two approaches to establishing such registers: according to different nosological forms and all hereditary pathology together. Theoretically, an overall register of hereditary diseases could be created, but because of the unwieldy nature of necessary information and large number of participants, it is unlikely that it would operate on a good methodological level. For this reason, preference is given to registers according to different forms. It is quite apparent that, in a number of instances, clinical investigation of causes of polymorphism alone is not enough. For this reason, there are also plans for molecular genetic studies of the nature of hereditary diseases (hepatolenticular degeneration, mucopolysaccharidosis, hemoglobinopathies).

Analysis of hereditary predisposition for diseases occupies a serious place in modern medical genetics. During the forthcoming 5-year period, research will be directed at identifying the elements of development of multifactorial diseases (concrete genetic markers and environmental factors). Of the genetic markers, antigens have been identified most often heretofore. Immunogenetics will continue to help clinicians, but there must be expansion of the spectrum of biological markers, specifically aimed at pathogenesis of concrete diseases. In store is the study of the structure of hereditary predisposition for diabetes mellitus, ischemic heart disease, rheumatism, essential hypertension and peptic ulcers, in order to identify concrete risk factors for development of these diseases. The relevant questions will be answered by using clinico-genealogical and genetic-epidemiological approaches and methods of mathematical modeling.

It is imperative to give more attention to such an important question as the significance of genetic factors to development of chronic diseases. Thus far, clinicians have underestimated the effectiveness of genetic approaches to the study thereof. They devote more attention to environmental factors. Evidently, geneticists must display initiative and actively cooperate with clinicians in the study of chronic diseases.

Congenital developmental defects are singled out as an independent section from the general problems of clinical genetics. This is related to the fact that they constitute a serious problem to public health because of the large share thereof in child and particularly perinatal mortality, hospitalization and disability among children. To date, it has been determined that the contribution of genetic factors to etiology and pathogenesis of congenital developmental defects, particularly multiple ones, is rather large (at least 50-70%). Improvement of methodological opportunities for studying genetics of congenital developmental defects has made it necessary to solve this complex problem speedily.

Under the 11th Five-Year Plan, studies will be pursued of the causes of clinical polymorphism and genetic heterogeneity of syndromes of multiple developmental defects. For this purpose, methods of clinical examination must be unified with regard to congenital developmental defects, including examination of relatives, studies of correlation between different developmental abnormalities, making use of simulation modeling. Comprehensive investigation of multiple congenital developmental defects will make it possible to prepare diagnostic tables and, on this basis, improve not only diagnostics, but prognostication of the risk to future offspring. Genetic analysis of congenital developmental defects is helpful in approaching some problems of genetics of human development. Even now, systems analysis of congenital developmental defects from the standpoint of genetics is possible on the basis of integrating experimental genetic, clinical genetic and pathomorphological approaches and data.

We must have knowledge not only about the clinicogenetic characteristics of hereditary diseases, but population-geographic patterns of their distribution in order to prevent hereditary pathology in the present and future generations. Questions of human population genetics on the medical level are interpreted in practical recommendations when analyzing the distribution of hereditary diseases. A new direction, which was formulated and validated by our scientists--population geography of hereditary diseases--is continuing to develop intensively. It takes into consideration geographic, ethnic and population factors that determine the incidence of hereditary pathology. This approach makes it possible to determine the "fate" of mutations and predict the incidence of hereditary pathology in future generations. Public health agents can plan the scope of specialized forms of care in accordance with the incidence of hereditary diseases.

The five-year plan provides for comparative studies of population structure and burden of hereditary pathology for urban and rural populations in two different regions (European part of the USSR and republics of Central Asia). It is not difficult to see that cross-comparison of population groups for parameters under study constitutes one of the models of population genetics used to determine the significance of the inbreeding coefficient, migration and isolation to the incidence of hereditary diseases. Aside from the theoretical

value of such data, they will be used to plot medical genetic maps of distribution of such hereditary diseases as hemoglobinopathy, erythrocytopathy, neurological diseases, mucopolysaccharidosis and eye diseases. Much attention will be devoted to investigation of the incidence of congenital developmental defects and the link between their appearance and environmental factors. Every branch of population genetic studies will use not only so-called field material, but electronic computer technology to store information and for simulation modeling.

Monitoring the intensity of the mutation process that produces new hereditary deviations occupies a substantial place in the prevention of hereditary diseases (which is the main purpose of medical genetics). This direction combines fundamental and applied research, which will be pursued under the 11th Five-Year Plan. It is necessary to study the quantitative patterns of spontaneous and induced mutation processes, particularly under the combined effect of environmental factors (radiation, chemical and biochemical). The existing methodological prerequisites make it possible to study this in human cells by recording chromosome aberrations and sister chromatid exchanges, as well as to assess the role of repair systems in determining the ultimate incidence of spontaneous and induced mutations. Studies of the mutation process in man, namely its most general characteristics, will require the use of mathematical methods and simulation (on a computer) modeling.

One of the most acute problems of our times is pollution of man's environment in the broad sense of the word. The question of long-term sequelae of this phenomenon in the form of mutations is particularly important. Monitoring the intensity of the mutation process can already be done in part, by means of assessing the mutagenic hazard of new factors in man's environment. In the preceding 5-year period, appropriate methods were developed, but studies must be continued, particularly with regard to combined [complex] evaluation of the mutagenic effects of physical and chemical factors in low doses, methods of setting standards for pollutant levels in the environment. There will be practical testing for mutagenicity of drugs and pesticides.

Long-term evaluation of the dynamics of level of hereditary pathology in human populations is an important question for clinical medicine and organization of public health care. This work should begin even now, so that trends can be demonstrated on the basis of accumulated data. The forms of record-keeping that exist in the public health system do not permit evaluation of the incidence of hereditary pathology; for this reason, under the 11th Five-Year Plan, work will be done to evaluate the suitability of considering chromosome anomalies, gene mutations and congenital developmental defects to monitor the incidence of hereditary pathology (genetic monitoring). It is quite apparent that this will require checking the monitoring system in specific population groups and development of mathematical approaches to modeling thereof. The prerequisites for such work have already been provided.

It was stressed in the decisions of the 26th CPSU Congress that there is a need to expedite introduction of scientific advances to practice. Medical genetic research has been projected from this point of view in the 11th Five-Year Plan. Development of methods for prevention, detection and treatment of hereditary diseases constitutes a large section of the applied part of the

entire program. In the future, everything should be directed at prevention of hereditary pathology. This applies in particular to the wide-spread diseases. From the organizational point of view, the following three sections of care for patients with hereditary pathology and their families are the most important: 1) mass-scale detection of hereditary diseases; 2) prenatal detection thereof in high risk groups; 3) medical genetic consultation.

In the last 10 years, various methods and programs, particularly of the screening type, were proposed in our country for mass detection of hereditary diseases. Many of them did not justify themselves in practical work. This is related to the fact that the reliability and economy of different programs for detection of the same diseases had not been compared in advance. At the present time, clinical geneticists are faced with an urgent task, that of offering precise recommendations--what, where, when and how to adopt methods--to public health agencies, rather than voicing their doubts about methods proposed by other authors.

We should like to call the attention of clinical geneticists to the need for developing methods of early detection of hereditary diseases that are manifested at a late stage, even if methods of preventive therapy have not yet been developed. The families involved could make a decision, after medical genetic consultation, concerning future birth of children, depending on whether prenatal diagnostic methods exist or not.

In view of the practical importance of the problem and knowhow of existing laboratories, several of the studies under the 11th Five-Year Plan will deal with new methods of diagnostic genetic anomalies of neuromediators, lipid, amino acid and carbohydrate metabolism.

Prenatal diagnostics is a vivid example of the most effective application of advances in medical genetics to public health practice. First of all, the main gap in organization of prenatal laboratory diagnostics in major cities should be filled, at first, perhaps, at obstetric and gynecological institutes. However, this does not eliminate the need for development of methods of diagnosing new forms and at earlier stages using chorion biopsy. Such studies will be conducted at several institutes under the 11th Five-Year Plan.

In the preceding 5-year period, the organizational principles of consultations were developed, a network of consultation offices was deployed, methodological recommendations for physicians were prepared and the training of qualified personnel was begun. The next problems of primary prevention of hereditary diseases require intensification of this direction of work. However, there are not only organizational, but scientific "liabilities." Thus, there are still few tables of empirical risk that are convenient for geneticist-physicians, recommendations have not been sufficiently worked out for advanced training of physicians in the field of hereditary pathology and dissemination of medical genetic information among the public.

Geneticists are also faced with such unsolved problems as principles for dispensary supervision of families with hereditary pathology, methods of picking up groups of pregnant women with a high risk of giving birth to a child with

congenital or hereditary pathology, distinctions of specialized consultations (neurological, ophthalmological, dermatological diseases).

The question of improving the effectiveness of scientific research is not an academic one. A State program has been approved to increase the effectiveness of scientific research in the field of medical genetics. It is imperative to intensify collaboration among scientists in different specialties so that they could reach the set goal together. The All-Union Scientific Society of Medical Geneticists could play a rather significant role in this regard.

It can be stated that good material and technical prerequisites, as well as qualified personnel, are available to fulfill the plan under the 11th Five-Year Plan in the field of medical genetics.

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GENETIC EPIDEMIOLOGICAL APPROACHES TO INVESTIGATION OF MULTIFACTORIAL DISEASES
IN PSYCHIATRY

Moscow VESTNIK AKADEMII MEDITSINSKIKH NAUK in Russian No 6, Jun 82
(manuscript received 16 Dec 81) pp 66-69

[Article by Ye. D. Krasik, A. I. Potapov and M. S. Ritsner, Siberian Branch
of the Institute of Psychiatry, USSR Academy of Medical Sciences, Tomsk]

[Text] At the present stage of research on biomedical problems, the search for new methodological approaches is acquiring paramount importance. The relatively rapid changes in periods of "methodological renewal" and "accumulation of facts" are the distinctive feature of the most intensively developing scientific directions in psychiatry, in particular clinical epidemiology, population genetics and genetic epidemiology.

There has been appreciable growth of interest in developing expressly these directions in recent years because of the theoretical and practical significance of such a major and complex problem as diseases with hereditary predisposition (multifactorial diseases). Analysis of the results of epidemiological and genetic studies in psychiatry have shown that there is a need to solve a number of methodologically important problems. With reference to the methodological aspects of genetic epidemiological research, we should dwell, first of all on a definition of the concepts of "epidemiology," "population genetics" and "genetic epidemiology."

Epidemiology refers to population studies for determination of the role of different factors in distribution and distinctions of manifestation of mass-scale infectious and noninfectious diseases.

Population genetics is concerned with the study of the laws that determine the genetic structure of populations and evolutionary factors that are active in the population. In other words, the subject of this discipline is referable to hereditary phenomena on the population level (N. P. Bochkov, 1978; Lee, 1978). Genetics that studies populations investigates the genetic traits of man (including hereditary diseases) in the aspect of dynamic balance between the mutation process and selection. However, when analyzing factors that affect the mutation process and selection, one must evaluate the same characteristics of populations that epidemiologists are concerned with (Neel and Schull, 1958). The study of mechanisms of distribution of hereditary pathology in populations with different structure is developing into an independent scientific direction,

which could be called "population geography of hereditary diseases" (Ye. K. Ginter, 1979) and referred to genetic epidemiology. Thus, genetic epidemiology is a section of epidemiology and medical genetics that deals with the nature and patterns of effects of population dynamics factors on incidence, origin and phenotypic polymorphism of noninfectious diseases among the population. Genetic epidemiology is directed primarily to the study of pathology in the population, whereas population genetics has broader tasks.

In recent years, the issues we have touched upon have become more and more often the subject of special debates, whose participants advance different views on the problems and tasks of genetic epidemiology. In the opinion of Abbey (1979), epidemiology will help geneticists who study human populations in determining the nature of genetic effects. In turn, genetics can be used by epidemiologists to determine the significance of a number of factors that affect manifestation of disease.

The clinical epidemiological studies conducted in psychiatry turned out to be a very fruitful approach to the problem. One can trace the evolution from empirical determination of frequency and some patterns of distribution of mental diseases to evaluation of the effect of different factors on these processes and, finally, detection of subclinical disorders according to the complexity of the objectives of epidemiological research. The epidemiological approach was also valuable in assessing the efficacy of rehabilitation measures, as well as planning and upgrading the multi-element system of medical care (N. M. Zharikov, 1972; Ye. D. Krasik, 1975).

Among the main mental diseases, those referable to the multifactorial group (schizophrenia, affective psychoses, epilepsy, chronic alcoholism and others) are encountered the most often; clinical epidemiological studies thereof made it possible to obtain new data characterizing the patterns of their distribution and phenotypic polymorphism.

For a long time, it was considered an axiom that the urban life-style is a factor that provokes manifestation of the schizophrenic process. To confirm this, data were submitted concerning the larger number of schizophrenics in cities, as compared to rural areas. However, special epidemiological studies and standardization of data according to age and sex refuted this point of view. It was found that this distribution of patients was not attributable to the influence of urban or rural life-style, but to the simple fact that the population in the age group of 16 to 25 years (the age at which there is the highest risk of schizophrenia) is considerably smaller in rural areas than cities. Our analysis also showed that there was no validity to statements that there is a higher incidence of schizophrenia in the socially lowest groups of society (Ye. D. Krasik, 1967).

At the same time, our epidemiological studies revealed that the incidence of schizophrenia is by no means the same in different microsocial occupational groups. Thus, schizophrenics are encountered 7 times more often among students on physicomathematical faculties than those on technical faculties. At the present time, we can find a selective sample to prove any hypothesis concerning the symptomatology, course and effectiveness of patient rehabilitation. However, only comparative epidemiological studies could provide an objective assessment of the facts.

Numerous studies of recent years have demonstrated some attenuation of the register of clinical manifestations of the schizophrenic process. However, the optimistic data concerning the change in course of schizophrenia and efficacy of rehabilitation programs require more specification. The fact of the matter is that, as a result of improvement of psychiatric care and change in the public's attitude toward it, many patients with process and periodic schizophrenia became included in the field of vision of psychiatrists. Expressly their rehabilitation created the illusion of drastic improvement in efficacy of therapy and course of the schizophrenic process. In spite of the decrease in share of patients with the "nuclear" form in the overall structure of recorded schizophrenia cases, the intensive indicators have remained on the same level for 30 years. Thus far, attenuation of gross psychopathological symptoms has not had an appreciable effect on the social and vocational prognosis for such patients.

Expanded epidemiological characteristics were recently obtained for epilepsy and chronic alcoholism. However, like those referable to schizophrenia, these epidemiological data are not usually backed up by family studies and, consequently, they do not permit analysis of the role of the genetic factor in etiology of the diseases in question.

Determination of the etiology of mental diseases requires investigation of the influence of the entire aggregate of relations between social and biological factors. I. V. Davydovskiy and A. V. Snezhnevskiy (1965) stressed that "Only knowledge of these relations will permit development of new, higher levels of preventive medicine." The etiological orientation of epidemiological research signifies a change from recording phenomena and their dynamics observed in a population to in-depth investigation of causative, including genetic, patterns. In terms of medical genetics, such a turn requires systematic investigation of the genetic and ecological bases of origin, distribution and polymorphism of mental diseases.

At the present time, genetic research in psychiatry is characterized by integration of traditional family and twin studies with genetic epidemiological and biological approaches (A. V. Snezhnevskiy and M. Ye. Vartanyan, 1979). The data obtained within the limits of such a strategy validate the hypothesis of hereditary heterogeneity of psychopathological disturbances, which admits the existence of various mechanisms of biological disturbances. One of the main tasks for clinical genetics of multifactorial diseases is to formalize the clinical characteristics of phenotypes studied and develop principles of differentiation into genotypically more homogeneous groups. In this respect, the traditional clinical-genealogical and twin approaches are invalid, since modern methods of multidimensional analysis require work with a larger number of unknown genetic parameters that are to be evaluated, which can only be done with genetic epidemiological orientation of research (V. M. Gindilis and I. V. Shakhmatova-Pavlova, 1979). The unfinished and contradictory nature of many findings and conceptions pertaining to genetics of schizophrenia, affective psychoses, epilepsy and chronic alcoholism is largely attributable to failure to take into sufficient account this methodologically important thesis.

For the time being, there have been only isolated genetic epidemiological studies in psychiatry. We can mention the work of Book (1953), based on

genetic psychiatric examination of an epidemiological nature, covering an extensive part of northern Sweden, as well as the comprehensive clinical genetic studies of V. M. Gindilis (1979). Scandinavian scientists have conducted twin studies of the epidemiological type (Tienari, 1963; Klinglen, 1964).

Genetic epidemiological studies of the main multifactorial mental diseases have not yet disclosed the structure of genetic susceptibility, and this is apparently due to the slow evolution of appropriate methods and models. However, the process of epidemiological and genetic research serves as a reliable prerequisite for extensive and methodologically correct genetic epidemiological studies in psychiatry.

The desirability of conducting such studies is related to development not only of the clinical epidemiological direction in psychiatry, but mathematical direction in medical genetics. These studies are needed for both obtaining representative data with utmost consideration of phenotypical polymorphism of the disease under study and determination of the population incidences and estimates of various phenes in order to then use the mathematical apparatus of multi-dimensional genetic analysis. By means of such analysis, it is possible to obtain the correct evaluations of contribution of genotype and environment to the origin of a disease, compare and evaluate various clinical (and other) systematics, search for pathogenetic markers of susceptibility, come closer to solving a number of prognostic problems of importance to medical genetic consultation. The genetic hypothesis of origin and polymorphism of multifactorial disease, consideration of which increases the informativeness of concrete biochemical, immunological, electrophysiological and other studies (V. M. Gindilis, 1979), is constructed on the basis of segregational analysis and testing of various phenotypic models (alternative, strictly continuous, quasi-continuous).

Thus, the interpenetration of a number of methodological approaches that have been tested in epidemiology and genetics is the only mutually beneficial process that consistently leads to formation of an independent scientific direction (genetic epidemiology). It can be assumed that systematic use and refinement of genetic epidemiological approaches to the study of the main mental diseases in the multifactorial group will yield new information about the mechanisms of onset, pathogenesis and essence of psychopathological disorders.

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CO-TRANSFER EFFICIENCY OF pAP38, pAP39, pAP41, pAP42 and pAP43 SEX FACTORS

Moscow BYULLETEN' EKSPERIMENTAL'NOY BIOLOGII I MEDITSINY in Russian Vol 93,
No 5, May 82 (manuscript received 17 Jun 81) pp 82-84

GIGANI, O. B. and PEKHOV, A. P., Chair of Biology and General Genetics,
Friendship of People's University imeni Patrice Lumumba, Moscow

[Abstract] The E. coli system was employed in studies on the capacity of the pAP38, pAP39, pAP41, pAP42, and pAP43 sex factors to act as co-transfer agents for several nontransmissible plasmids. The results showed that all of these factors, in the E. coli systems tested, including the F'lac plasmid, co-transferred the following nontransmissible plasmids, pSF2124, pMR5, and SuSm. In addition, pAP42 and F'lac also co-transferred pBR322, while pAP41, pAP43 and F'lac co-transferred plasmid pAPCYC184. None of the factors tested, including F'lac, could co-transfer pS C101. Although the mechanisms of co-transfer remain largely unclear, it is likely that the transmissible plasmids are incorporated into the nontransmissible plasmids. References 5:
2 Russian, 3 Western.
[377-12172]

MEDICAL DEMOGRAPHY

UDC: 614.2+614.1:312

PUBLIC HEALTH: TRENDS AND RESEARCH TASKS

Moscow VESTNIK AKADEMII MEDITSINSKIKH NAUK SSSR in Russian No 11, Nov 81
(manuscript received 15 Jun 81) pp 33-40

[Article by Yu. P. Lisitsyn and V. K. Ovcharov (Moscow)]

[Text] In the proceedings of the 26th CPSU Congress, it is stressed that one of the main tasks for economic and social development of our country in the next 10 years is to implement an effective demographic policy, as well as a system of measures to prolong the life and employment of people, to strengthen the health of the public.

Studies of medicodemographic trends, which are related to this task, constitute the main elements of evaluation of current public health and, along with data pertaining to morbidity rates, they constitute the foundation for control and proportional development of public health.

In our times, interest in public health problems has keenly increased in view of the known decline in rate of formation of manpower resources in our country. For expressly this reason, the sociohygienic approach is being used more and more for analysis of internal links between the system of the public and its health and the environment with its deciding socioeconomic foundation--the public health resources. The solution to this problem must take into consideration the distinctions of life-style, demographic behavior of different population groups, i.e., social consequences of scientific and technological progress, which determine the health of the people. Under modern conditions, a thorough analysis of health trends and reproduction provides the main prerequisites for validation of an active demographic policy.

The study of public health, its age-sex, social, professional, ethnic and other groups, is one of the main tasks for the research of sociohygienists and public health organizers, as well as representatives of other medical disciplines.

Soviet medicine has always held a leading place in the study of public health; already during the period of Zemstvo medicine, methods for complex [combined] examination of the public were developed for the first time anywhere in the world, and this pertained primarily to diseases that have retained their significance to this day. Soviet scientists created a system of parameters, which comprehensively analyze and assess public health. It makes extensive use of mathematical, statistical, sociological methods, equipment and procedures of

modern computer technology, electronic computers and methods referable to the systems analysis approach.

In the USSR there is a State statistical service, which includes registration of demographic indicators and certain health indicators, on the basis of which and of data from so-called in-depth health statistical studies assessment is made of the changes in public health status. Epidemiological and combined socio-hygienic studies of public health are acquiring increasing importance, and they permit demonstration of the dependence of health indicators on working and living conditions, patterns of its social determination, risk factors and population groups subject to a higher risk of disease, which is particularly important to validation and implementation of preventive measures. In-depth health-statistics, combined sociohygienic, clinicosocial (or combined sociohygienic studies of patient groups) and epidemiological studies have proved their role in representative samples, including the so-called cluster ["nest"] method, stage-by-stage and family-by-family studies, use of paracopies and other methods of making comparisons. In our country, theory and practice of medical-health statistical studies of samples have been developed, which could be the basis for a system of monitoring the dynamics of the most important indicators of public health.

We proceed from the fact that public health is not only a biomedical, but a social category, since "man is a social being, the ensemble of all social relations, within and by means of which his social qualities are formed, his innate strength and dispositions develop or, on the contrary, are suppressed. Man receives health as a gift from nature in a certain sense. But, whether this gift will multiply or be mercilessly exploited and depleted depends on society. The health of man is an inalienable element of social assets, and how these assets are distributed, preserved, used and reproduced depends on society."*

The social determination of public health is not only the prerequisite for studying it, but the most important result of sociohygienic and epidemiological studies, which demonstrated that health indicators depend on social conditions and factors, on the direct influence of life-style. Aside from its scientific and theoretical significance, this conclusion has great social and political importance. It points to the advantage of the socialist system and social policies in the area of public health that are being implemented by the CPSU and the Soviet government. This is manifested, in particular, by the faster improvement of public health indicators in the USSR and other socialist countries, as compared to capitalistic countries, and particularly by the social homogeneity of public health in the USSR, in contrast to the sharp social heterogeneity of public health in capitalistic countries. In our studies, including those of families, we failed to demonstrate any appreciable differences in public health indicators as related to belonging to social strata and classes, as well as such a complex [combined] criterion as material security, income (per person or family wages). For example, the differences in morbidity rate involving temporary disability did not exceed 10-20% among individuals referable to different budgetary groups. At the same time, foreign authors report vivid differences in health indicators between individuals referable to different social groups in a capitalistic society. For example, according to official data in the so-called "White Book" (Washington, 1971), the incidence of visual

*KOMMUNIST, No 9, 1979, p 42.

disturbances was 8.7 times higher, arthritis and rheumatism 6.8 times higher, neuropsychiatric cases 6.3 times higher, cardiovascular diseases 4.5 times higher, essential hypertension 6.1 times higher and disturbances referable to the skeletomuscular system 3.6 times higher in families with low income, as compared to those best provided for, referable to the so-called first social class. According to some data, infant mortality rate in Great Britain constituted 10.0 per 1000 neonates in families referable to the first "social class" and 28.0 for those in the fifth "social class" in 1972. The drastic social heterogeneity of public health in capitalistic countries is a reflection of social heterogeneity of capitalistic society.

The social homogeneity of health state of the people of the USSR is also manifested by a tendency toward closer health indicators among individuals engaged in physical and intellectual labor, urban and rural population, different ethnic and social groups. This trend is one of the expressions of the increasing social homogeneity of socialist society.

The social determination of public health is also manifested in such a fundamental phenomenon as transformation of type or profile of pathology, which has occurred in our country in a historically unprecedented short time, in essence in the lifetime of one generation. In the place of pathology of the epidemic type, which we so named because of prevalence of infectious diseases, including epidemic ones, there is now pathology of the nonepidemic type, which is characterized by increasingly chronic nature of pathology, the prevailing incidence of chronic nonepidemic diseases in the structure of the mortality rate and their ever growing share in the structure of morbidity. Of all deaths, 90% or more are due to only four groups of diseases in economically developed countries at the present time (cardiovascular, malignant neoplasms and accidents, respiratory diseases). This also applies to the USSR, where only two groups of diseases (cardiovascular and malignant tumors) were the cause of 65% of all deaths (1978), with 51% share referable to diseases of circulatory organs and 14% to oncological lesions.* Since the turn of our century, mortality due to infectious and epidemic diseases dropped to 1/20th-1/30th, while that attributable to cardiovascular diseases and malignant neoplasms rose by 3-3.5 times in such countries as the United States, Great Britain, France, Sweden and others. Against the background of a substantial decline of mortality rate (to one-half in economically developed countries and to one-third in the USSR in the last 50-60 years) and an appreciable trend toward reduction of overall morbidity in the USSR in the same period of time there was not only a radical regrouping of the structure of these indicators, but a tendency toward approximation of the structure of mortality and morbidity (for example, in the last 20-25 years, cardiovascular diseases "moved" from 7th-8th place in the structure of morbidity to 2d-3d place). The incidence of chronic, nonepidemic diseases, particularly cardiovascular, nonspecific diseases of the lungs and respiratory tract, endocrinopathy, allergic diseases, accidents and, first of all, transportation trauma has increased and is continuing to rise. Thus, studies of incidence of cardiovascular diseases (Ye. I. Chazov; I. K. Shkhvatsabaya; V. A. Nesterov; Yu. P. Lisitsyn; Ye. G. Protsek and I. D. Bogatyrev; V. K. Ovcharov, and others) indicate that they are demonstrable in 25-30% of the population,

*VESTN. STATISTIKI, No 11, 1979, p 67.

particularly among the elderly and aged. The significance of a number of infectious diseases is growing, primarily viral diseases, including influenza and influenzal pneumonia, infectious hepatitis and adenoviral infections.

The fact that pathology is growing chronic renders particularly acute the problem of finding the etiopathogenetic factors in common to a number of diseases. It has been demonstrated that there are few risk factors in common for diseases that constitute the foundation of nonepidemic pathology, among which the role of smoking, drinking, unbalanced diet, hypertension and hypercholesteremia, hypodynamia, psychoemotional reactions, environmental pollution and others is being shown. This circumstance makes it imperative to be more decisive in working out methods of forecasting diseases and primary prevention, which should be the duty of every therapeutic and preventive institution, and primarily the institutions that render primary medical and health care (walk-in and polyclinic facilities, sanitary and epidemiological stations, maternity, emergency and first aid services) as the main element of safeguarding and improving public health.

Formation of the nonepidemic type of pathology and the conception, which is closely related to this process, of pluricausality of diseases that make up its basis stresses the need for active work on medical-sanitary and socio-medical aspects of life-style, which directly determines the level and structure of public health and should be used to develop prevention and dispensary care. The results of sociohygienic studies (Second Moscow Medical Institute, All-Union Institute of Social Hygiene and Public Health Organization imeni N. A. Semashko and others) are indicative, in particular, of expansion of dispensary care with consideration of social and demographic characteristics.

The trends of public health are closely related to typical demographic processes. In our country, the birth rate declined systematically up to 1970. This decline was particularly perceptible in the 1960's. It reached the minimum level of 17% in 1969, having dropped by 45.5%, as compared to 1940 (31.2 ‰). In subsequent years, this indicator started to rise and constituted 18.2 per 1000 population in 1979. This is rather high, as compared to a number of economically developed countries, and it provides for optimum development of the population in our country, which is required under modern conditions of expanded reproduction.

For the sake of comparison, let us mention that, in 1977, the birth rate was 15.5 per 1000 in Japan, 13.3 in the United States, 14.0 in France, 13.3 in GDR, 11.6 in Sweden and England, 9.5 in FRG. In the FRG, there is virtually negative population growth.* And it is important to bear in mind that, already since 1970, the birth rate is maintained mainly at the expense of first-born infants, the share of which has increased from 38% in 1959 to 47% in 1979, due to some increase in number of second births among mothers up to 25 years of age, younger age of marriage and increase in number of married couples. The share of third and subsequent order births, which provide for expanded population growth, continues to decline.

*"National Economy of the USSR in 1979. Statistical Guide of the USSR Central Statistical Administration," Moscow, "Statistika", 1980.

A distinction of recent years is that formation of families ends considerably sooner and the opportunity appears of even greater involvement of women in social labor. Large cities serve as an example, where the share of women (for example, in Moscow) constitutes 56% of all those employed. Because of the early termination of family formation, the period of protection against pregnancies is considerably longer, there is increased importance of effective contraceptives and abortion, if there are no adequately effective contraceptives.

Under conditions of considerable birth control, the health of parents and particularly future mothers, as well as possibility of their sterility, is of special significance to public health. Recently, data have been published indicating that up to one-quarter of the women in other countries cannot become mothers because of sterility.

It must be noted that sociohygienic and medical work, which is instrumental in improving population growth conditions, safeguarding mother and child health becomes meaningful only if there is a high degree of differentiation of these measures in different regions of the country, primarily with consideration of national and domestic distinctions related to birth rate. While the average birth rate in 1979 was 18.2 per 1000, it constituted 13.8 in Latvia and 37.7 in Tajikistan.

There are drastic differences in both the birth rate ["intensity" of birth rate] and structure of the groups that give birth. Thus, in the republics of Central Asia, every 10th women at the age of 40-44 years gives birth to 6-8 children, whereas in other parts of our country the figure has long since been limited to 1-2 children. Hence the distinctions, to some extent, in the work of mother and child care services in Central Asia, where the need for them is considerably greater than in other republics.

A study of the trends of birth rate has shown that there are mainly two groups of factors that play a part--demographic and socioeconomic, which include: age and sex composition of the population, marriage rate, duration of married period, birth order, extent of family planning, as well as extent to which women are involved in social production, level of urbanization, family income, housing conditions, education, ethnic group, availability of children's institutions, age at which parents were married, etc. It has been established that socioeconomic factors do not have a direct influence, but are mediated by the consciousness of people, the decision to have children. Ultimately, this is manifested by the extent of family planning of children.

The decline of birth rate is also manifested by the process of so-called aging of the population, which has the most substantial influence on the change in nature of pathology. The overall population of the USSR increased by 8.6% between 1970 and 1979, whereas the number of individuals over 60 years of age increased by 18.3%. In recent times, the process of population aging is being experienced by many countries, in which the share of people over 60 years old constitutes up to 20-24%.

In our country, there is an average of only 2-3 men per 7-8 women in age groups over 60 years. For this reason, medical care for single women is

acquiring increasing importance. Mainly chronic diseases and essentially only two causes of death--circulatory system diseases and malignant neoplasms--are inherent in individuals 60 or more years of age. It should be noted that the older age group includes virtually all participants of the Great Patriotic War. For this reason, in the opinion of some authors there has been some rise of death rate among population groups who have experienced the hardships of war.

In characterizing the death rate, we must mention the enormous socioeconomic transformations which, along with general scientific and technological progress and development of public health in our country for tens of years, were instrumental in lowering it significantly. In 1964, the USSR death rate dropped to 6.9 per 1000 population, as compared to 29.1 in 1913. Since 1965, there has been a trend toward rise of the general, or gross, death rate. The rise of the general death rate to 8.2 per 1000 in 1970 and to 10.1 per 1000 in 1979 was attributable essentially to an increase in share of older age groups, who survived, thanks to public health advances, the formerly high risk of death at a young age and now determine the higher mortality indicators for the population as a whole.

The rise in mortality rate in recent years is related mainly to diseases of the circulatory system and accidents. The death rate due to circulatory system diseases increased by 22.3% in the period from 1965 to 1979 according to standardized indicators, in urban areas and by 54.5% in rural regions; a rise occurred in all of the Union republics, and it was related chiefly to ischemic heart disease and vascular pathology of the brain, which account for 88% of all deaths due to cardiovascular diseases. With reference to other causes of death, malignant neoplasms are singled out as the second main cause of death, whose dynamics are distinctive. On the whole, there has been some decline, mainly referable to the female population, in mortality due to malignant neoplasms. It is related essentially to a decline in incidence of cancer of the stomach and uterus. On the other hand, there has been an increase in cases of malignant neoplasms of the lung, breast, intestine, hemopoietic and lymphatic systems. There are also some distinctions to the dynamics of respiratory organ diseases as cause of death. Until recently, there had been appreciable rise in mortality due to this group of diseases; then the rise of indicators stopped and for the last few years some decline of mortality has been reported.

A trend of paramount importance in recent times is that the mortality rate has been higher since 1972 in rural areas than in urban ones. This is particularly marked among children from 1 to 4 years old. The most marked differences are referable to certain causes of death. Thus, in 1979, the mortality level due to diseases of respiratory organs was almost twice as high in rural areas as in cities. Aside from the distinctions of living and working conditions in rural areas, these differences are perhaps related to a difference in level of availability and quality of medical care of the rural population.

The increased gap between mortality rates for men and women is an important trend in mortality processes. The standardized indicators of male mortality were considerably higher than female mortality, and the average life expectancy of women was longer than for men. This is related to the participation of men in the war, performance of the heaviest and most health-endangering types of work, and particularly the prevalence of bad habits among men.

Regional differences in mortality rate and distinctions of causes of death are quite important. The widest differences between regions of our country were referable to such causes of death as diseases of respiratory and digestive organs, infectious and parasitic diseases. Living conditions, difference in extensiveness of bad habits and (to some extent) medical care are noted among the causes of regional distinctions of mortality rate.

The foregoing also applies largely to the problem of child mortality. Considerable differences have been noted in Union republics in levels of child mortality, which is largely attributable to the still persisting living and sanitary-hygienic living distinctions, local customs, which are manifested by improper care of children, feeding, attitude toward hospitalization and others. The main causes of infant deaths in the first year of life were diseases of respiratory organs, perinatal causes, infectious and parasitic diseases, as well as congenital anomalies, in the nation as a whole (1979).

Along with the above factors, investigators relate changes in mortality rate to growth of urbanization, intensification of transportation, immobility of people, failure to adhere to proper schedule and caloric value of nutrition, atmospheric pollution. There has been much research done on these matters. In such studies, much use is made of mathematical and statistical procedures, which permit isolation of the strongest factors out of an entire set, which numbers up to 20-30 factors. The importance of these studies is growing in particular, in connection with the fact that these factors are involved in different combinations in different parts of the country, which implies that different measures are needed to strengthen the health of the people, primarily improvement of organization of therapeutic and especially preventive care.

Scientific research has proven the feasibility of lowering mortality under our conditions, which is provided, in particular, by the wide scope of preventive physicals and cancer control measures, which resulted in an almost 10% decline of mortality referable to malignant neoplasms, as compared to other countries.

Deeper investigation of morbidity of the population is also a foundation for further achievement with regard to improving public health indicators and demographic processes, primarily lowering of the death rate. In recent times, there has been a substantial decline in incidence of infectious and other acute diseases, and among them influenza and acute respiratory diseases have taken a prominent place. In a large city, an average of up to 40% out of 1200-1600 primary requests for attention per 1000 population are referable mainly to acute respiratory diseases. Diseases of the circulatory system have shifted from 5th-6th place, which was the case 30 years ago, to 2d-3d place. Trauma and poisoning, diseases of the nervous system and sense organs, diseases of digestive organs, infectious and parasitic diseases are also mentioned among the most frequent causes of seeking medical care. Follow-up medical examinations of representative population groups offer considerable additional information in the area of cardiovascular diseases, pathology of the eyes, neuropsychiatric diseases, skin diseases and some diseases of digestive organs and the genitourinary system. The concealed part of pathology makes it also necessary to develop more effective means of early detection, as well as more effective means of treatment, since the new cases of pathology picked up during medical examinations have often already been cause to see a

doctor, but then escaped his attention for a long time, for different reasons, and progressed to stages that were difficult to treat.

In addition to aging of the population, the structure of morbidity is being determined more and more by the life-style, behavior and such factors as urbanization. In large cities, for example, hypertension and myocardial infarction were reported rather often. Due to air pollution, the risk of diseases of the respiratory organs has risen.

Our country has achieved a high level in the organization of prevention and therapy of the most important non-epidemic diseases. The structure of morbidity became close to that of pathology in the most economically developed countries, after considerably faster eradication of mass scale epidemics and social diseases. Expressly this created the false impression of supposedly increasing convergence of countries with different socioeconomic systems.

However, the internal [domestic] nature of this phenomenon varies. Socialist public health care has coped with the consequences of capitalism many times faster than any other country and, on the example of the system of cancer control, mental health care, development of cardiological care, convinces us of the existence of considerably greater reserves in the study of the nature of chronic diseases and use of all advantages of State public health in the control of these diseases. The similarity of pathology among different population groups--social heterogeneity of health status--is the radical distinction of our system. At the same time, the process of having pathology become similar in urban and rural areas, in different republics and other population groups of our country depends largely not only on the same socioeconomic possibilities, but proper utilization thereof in a manner that is beneficial to health. The life-style is more and more often present as an intermediate link characterizing this process of utilizing material well-being in the interests (and sometimes in spite of the interests) of the health of different population groups. For this reason, further advances in strengthening the health of the people are closely linked with both the study of the patterns of hygienic behavior of population groups, level and structure of satisfying material and spiritual needs, as well as development of a system of indicators characterizing public health proper and behavior of these population groups with regard to their health.

In addition to the known indicators of public health, increasing use is now being made of such positive factors as widening the family budget, expenses for cultural needs, tourism and recreation, higher grade foodstuffs, consumer goods, making time available for activities that improve health. The same interest is being shown in an increasingly closer investigation of food and time budget in families, which demonstrate beneficial conditions for increasing concern about health, physical culture and sports, fuller use of the entire system of therapeutic and preventive measures that are offered by public health institutions. Thus, a hygienically correct life-style and appropriate environmental protection become deciding factors for utmost utilization of all of the advantages of socialist public health to strengthen the health of the people.

This advances new requirements with respect to improvement of theoretical and, particularly, methodological work in the area of social hygiene and public health organization. A thoroughly planned system of test, probing surveys that are not large in scope but sufficiently representative for different regions of the country would permit making use of their findings as the scientific foundation for development of public health care, with due consideration of regional distinctions in population structure, health, life-style and organizaing medical care to conform to these distinctions.

Investigation of the health status of different populations groups, which still differ considerably in their condition from other groups, requires much attention. Migratory groups merit more thorough investigation. Increasing attention is being drawn to the study of differences in medicodemographic characteristics of population groups differing in level of education, groups referable to different occupations and particularly those differing in cultural level.

We must stress the transient nature of the concept of culture with reference to the health of the individual and different population groups. According to many features, what previously distinguished different population groups referable to the more cultured strata was associated with some factors that had an adverse effect on public health. In recent times, there are processes, particularly abroad, with which it becomes obvious that, along with improvement of well-being of some population groups, they are acquiring negative habits (diminished physical activity, wider prevalence of smoking, wide availability of alcoholic beverages, etc.). For this reason, one should pursue broad educational work, even now.

Problems of marriages between close relatives, student health, problems of elderly primipara and causes of higher fertility among mental patients merit more thorough investigation. It is imperative to pursue more thorough studies of the health of offspring of drinking and smoking parents. Questions of the health status of young couples, as well as problems such as further decline of widespread social diseases, in particular, tuberculosis, should occupy a special place in studies. There are facts that indicate that, even when incomes are good, there are considerable difficulties in lowering the incidence of tuberculosis, which are related to incorrect behavior, delay in seeking medical attention, failure to follow appropriate instructions and disorganized domestic life, particularly among young women, with high incidence of bad habits, which prevent the recognized main socioeconomic factors from exerting an effective influence.

All of these problems are mostly referable to the competence of specialized clinical institutes, the sociohygienic direction of whose work will, no doubt, be a guarantee that concrete measures will be worked out for development of public health care. The problem of preparing and implementing combined special-target programs of research on the health of the public is growing increasingly urgent.

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MEDICINE

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COMPUTER USE FOR ANALYSIS OF POLYCLINIC SERVICE PERFORMANCE

Moscow SOVETSKAYA MEDITSINA in Russian No 4, Apr 82 (manuscript received 10 Feb 81) pp 80-82

[Article by V. N. Savel'yev, T. V. Krupina, I. D. Burchakov, V. A. Kostromin, L. D. Torkhova and R. A. Lodygina, Izhevsk Medical Institute]

[Text] Polyclinic institutions require reliable information about public health status and morbidity. This information is the basis for planning future activity of polyclinics, provided it is processed rapidly and at the proper time.

However, the existing ways and means of processing information about the health status of the public, which are based on the use of manual labor, take up much of the time of qualified medical personnel. The productivity of such work is quite low, while the reliability and completeness of the received information do not meet the requirements, for which reason there is a decline in efficiency of therapeutic and preventive work. The same causes are at the basis of the fact that it is impossible to investigate the effectiveness of therapeutic and preventive work during the entire year and inspect [check] the performance of different elements of polyclinics. There is an objective need to search for and use new methods for gathering and accumulating data, to process and make an in-depth analysis of the information received as speedily as possible, and this can be done by introducing into polyclinic practice the optimum technology for recording, gathering, storing and processing data with the use of computers.

In preparing the "Polyclinic" information system, the Computing and Information Center of the Udmurt Ministry of Health proceeded from the requirement of speedy reimbursement of expenses with adherence to the principle of gradual [in stages] attainment of the end goal. Proceeding from assessment of actual feasibility, the immediate and practically attainable goal at the first stage consisted primarily of using computers to provide reliable and optimum recording, accumulation, processing of and immediate access to information about all aspects of work of outpatient polyclinic services in Udmurtskaya ASSR.

The main base data for implementation of such a system are contained in the traditional statistical record forms, but the documents themselves are not

suitable for computer processing. For this reason, the task at the first stage consisted of working out new, more technological input documents, developing a set of algorithms and programs that assure reliable, effective and deeper processing of base data, as well as development and trial of new output documents that offer more fullness and clarity of analytical information reflecting the therapeutic and preventive work of this republic's polyclinic services. There must be ready access to output data. A most important task at this stage was also to train medical personnel to work with the new documents, analyze well and make good use of new data in their practical work.

Two-year operation of the subsystem for ongoing record-keeping and analysis of polyclinic performance shows that all of the tasks put to it were performed.

The tasks of this subsystem are to automate records of physicians' work and performance of polyclinic departments; recording overall morbidity and morbidity involving temporary disability at therapeutic and preventive institutions, shops [of plants], sectors, with consideration of occupation, sex and age; automated preparation of reports on polyclinics.

Since the existing record forms, No 25t, 25v, 39 and 30 are not technological enough and unsuitable for computer processing, a document was developed that did not have these flaws and contained all of the data contained in the above-mentioned forms, as well as data required to perform the task of the "Polyclinic" subsystem. In developing this form, which was named the "admitting [receiving] stub," due consideration was given to the need to assure minimal time and labor to fill it out, adequate simplicity and convenience, clearness of entries; formalization of recorded information so that data could be transferred to data-carrying equipment and then processed on a computer; completeness of base data, elimination of need to use forms No 25t, 25v, 39 and 30; arrangement of data on the form in such a manner as to conform to the technological order of filling it out in all sections and for maximum convenience of transfer of data to punched tape.

The stub is in the form of a questionnaire, and there is a specific place for each tag [sign]. All of the tags contained in the stub can be divided into three groups: 1) identification; 2) diagnostic; 3) functional and organizational.

Classifiers are an important element of furnished information. The subsystem makes use of codes for the patients' place of work, occupation, diagnosis in accordance with the nomenclature, physicals, physicians, etc. The work schedules of physicians, with indication of number of hours worked over a specific period, are used as ongoing [operative] information in the subsystem. Rosters of polyclinic physicians, with indication of list number of specialty, lists of therapeutic and preventive institutions and territorial districts are used as standard and reference information.

At the present time, physicians of polyclinics and management receive 13 types of output documents as a result of data processing.

At the start of the routine cycle of gathering information, the identification part of the stub is filled out in the registry office or preliminary [before

being seen by a physician] receiving office for primary patients and by the nurse when another visit is scheduled. The diagnostic part is filled out by the attending physician. If a medical certificate [for sick leave] is issued, the physician writes down the date it was issued. After seeing patients, all stubs are handed over to the medical statistics office. There, they are stapled ["stitched"] and transported to the computing and information center for daily processing in the department of data preparation, where the information is transferred to a computer carrier.

There are provisions in the system for programmed checking of base data, along with visual checking when information is received by operators, for which reason it was possible to obtain a drastic reduction in number of mistakes in input data, and they constitute no more than 0.1-0.2%. The vast majority of these errors are detected and corrected in the course of the technological process, so that they do not affect the reliability of the information obtained.

Let us give a few of the results of analysis of experience in operating the subsystem. Adoption of the subsystem of ongoing record-keeping and analysis of the performance of 14 polyclinics on the basis of the standardized "admitting stub" made it possible to discontinue use of the previously mandatory record forms No 25v, 25t, 39 and 30. As a result, less time was spent by polyclinic physicians to fill these and other documents. Thus, while the physician spent 2.5 ± 0.5 min per patient to fill out various papers before introduction of the subsystem, it decreased to 1 ± 0.3 min after. As a result of this alone, the useful time spent by a physician on seeing a patient increased by 1 min per patient. This means that about 28,800 hours of physicians' time with patients was gained in a year in the 14 polyclinics, which corresponds to 19 physicians' salaries. Ongoing information about the work load of physicians makes it possible for polyclinic management, as well as the physicians themselves, to promptly alter their schedules for work pertaining to other duties (dispensary care, preventive examinations, health education work). The subsystem made it possible to obtain all of the polyclinic record indicators in an automated fashion using computers. This relieves all specialists of uncreative operations and the traditional practice of preparing reports, which used to take a significant part of their work time.

The availability of additional information improved analysis and made it possible to assess polyclinic work. District and shop physicians were able to analyze prepared and reliable data on overall morbidity based on frequency of seeking attention. The data on individual morbidity made it possible to detect "threatened" groups and categories of patients who should be under dispensary observation at an early time. It has become possible to make long-term plans for the work of polyclinic services; the work rhythm at institutions has improved, wise use is made of manpower resources and polyclinic specialists are performing a larger volume of work.

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REPORT ABOUT SIXTH INTERNATIONAL SYMPOSIUM ON ELECTROSTIMULATION

Moscow SOVETSKAYA MEDITSINA in Russian No 4, Apr 82 pp 119-120

[Article by V. V. Sigayev (Moscow)]

[Text] The Sixth International Symposium on Electrostimulation convened from 24 to 28 September 1981 in Al'bena (Bulgaria). The First International Symposium on Electrosleep and Electroanesthesia convened in 1966 in Graz (Austria), and the international society of the same name was then founded. This society had as its purpose dissemination of information about the effects of electric current on various parameters of the human brain through external electrodes, for therapeutic purposes (electrosleep) and anesthesia (electroanesthesia).

In view of the intensive development of use of electricity on different systems and organs of man (electroacupuncture, local electroanesthesia), at the next meeting of the symposium in 1978 the society was renamed as the International Electrostimulation Society.

Representatives from seven socialist and nine capitalist countries gathered at this symposium. Most of the participants were organizers of the symposium and representatives of the Soviet school of electrosleep. It should be recalled that electrosleep, as a method of nonspecific cerebral therapy, emerged in the USSR as far back as the 1940's-1950's, and is justifiably considered the "Russian method" all over the world. Expressly this was emphasized in the scheduled paper delivered by Prof V. B. IVANOV of the Varna Medical Academy, vice-president of the International Society. He noted that Bulgarian researchers and physicians directly continued [followed] the ideas of the founders of this electrosleep method--V. G. SERGEYEV, N. M. LIVENTSEV, V. M. BANSCHIKOV and others. At the same time, he called upon the participants to search for the relationships and common patterns of different electrotherapy methods, such as electrosleep and electroacupuncture, since both attenuate drastically the body's reactions to various nociceptive stimuli, which is related, in particular, to "discharge" of enkephalins into blood. Most papers dealt with the use of electrosleep in combined therapy of various diseases.

E. M. LEYZEROVICH (Moscow) reported on reduction of duration and longer remissions in patients with diverse psychiatric pathology treated by conventional drugs combined with electrosleep. Success with electrosleep was discussed by GALABOVA et al. (Bulgaria), PADOVA et al. (Bulgaria), TODOROV

(Bulgaria) in the treatment of various neurotic states, N. Yu. GILINSKAYA et al. (Moscow) in the treatment of logoneurosis and Ye. I. KULIKOVA-LEBEDINSKAYA et al. in the treatment of cardiophobic neurosis. These papers are a reflection of the traditional use of electrosleep with regard to form (pulsed, square-wave) and frequency--130-160 Hz. The efficacy of using expressly this mode of electrosleep in the treatment of essential hypertension was discussed in the paper of N. A. KOSTYUKHINA et al. (Moscow). In addition to square-wave pulsed current, NICOLOVA et al. (Bulgaria) used a combination of pulsed and square-wave current in the treatment of neurotic states. The same problem, i.e., electrosleep therapy of psychopathic and neuropathic states, was the topic of a film submitted by WAGENEDER, president of the International Electrostimulation Society.

In the discussions, Prof A. P. CHUPRIKOV (Voroshilovgrad) stressed that there is consistent worsening of the condition during electrosleep therapy, which should be interpreted as a manifestation of the phasic nature of electrosleep. S. R. ROYTENBURD (Moscow) discussed a new direction of use of electrosleep in his paper, "Preventive Use of Electrosleep to Improve Work Capacity of Railroad Dispatchers and People Engaged in Mental Work." This author demonstrated, using extensive material, that electrosleep eliminates to a significant extent fatigue, improves attention and normalizes arterial pressure in people engaged in intensive intellectual work, i.e., it is an effective nondrug method of preventing neurotic states.

In a paper entitled "The Role of Electrosleep in Combined Therapy of Glaucoma Patients," L. F. BELASH (Moscow) reported on the great efficacy of electrosleep: significant reduction of dosage and amount of drugs given, while ocular pressure remained more stable for 3 or more years.

Several papers dealt with use of electroacupuncture in the treatment of bronchial asthma (SOPIDO, Hure), vegetovascular dystonia (SANDU, Yugoslavia), pain syndromes (P. Ya. GAPANYUK, Moscow). The paper of I. V. KOTLYAR (Moscow) discussed the combined use of pulsed and sinus-wave current in treatment of peripheral paralysis of the lower limbs. For the first time at symposiums on electrostimulation, a paper was delivered by GRUNNER (CSSR) on use of magnetic fields in the treatment of severe cephalalgia. The paper of CARL-SHMIDT (England) on treatment of drug addicts with electroacupuncture aroused interest; this speaker proposed a method which consists of having the patient choose parameters that are "comfortable" for him by means of a portable unit. MONRATT (CSSR) proposed a nociceptive (mandatory!) method of stimulating the forearm with the use of electrodes that are in wide use in physiotherapy for treatment of chronic alcoholics. Yu. V. SEREGINA et al. (Rovno) reported on the treatment of cerebral paralysis with a combination of pulsed current and magnetic field. These authors obtained high efficacy (up to 80-85% recovery) within a relatively short time. They believe that they reach the neuroglia and that the destabilization stage (exacerbation) is mandatory in a number of patients when this technique is used.

Several papers dealt with refinement of various electrostimulation methods. BENGESESSER (FRG) proposed stimulation of the peridural space by inserting an electrode in it (the technique for this is the same as for peridural anesthesia)

for treatment of multiple sclerosis; GRACONIN (Socialist Federated Republics of Yugoslavia) shared his extensive experience in stimulating nerve trunks of the limbs in the presence of paralysis of diverse etiology, noting that the best effect of restoring function of the extremity is obtained following trauma; HOCHMAIR-DESOYER et al. (Austria) submitted data on patients who were absolutely deaf and who have been using hearing aids for 3 years now, which have electrodes implanted directly in the cochlear nerve; GUTTLER (GDR) touched upon technical aspects of percutaneous stimulation of nerve trunks in the presence of chronic pain syndrome; this author noted that the best results were obtained at current frequency of 100 Hz, pulse duration of 0.2 ms and power of up to 40 mA.

A. A. DZHABIYEVA (USSR) discussed in her paper the use of pulsed current with anesthetic parameters as an element of general anesthesia for oncological patients. Data were submitted on a better proportion of stressor hormones (ACTH, somatotrophic hormone, cortisol) during surgery using electroanesthesia than with the conventional method of neuroleptic analgesia.

The symposium commented on the unquestionable achievements of electrostimulation, the possibility of using such methods well in diverse branches of medicine and the need to develop these methods in both the clinical and technical direction. A decision was adopted to request that the proper [authorized] organizations of the USSR convoke the next, seventh, international symposium on electrostimulation in the fall of 1984, in Kislovodsk. The symposium elected Prof. V. M. Bogolyubov, director of the Institute of Balneology and Physiotherapy, as vice-president of the society from the USSR.

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CURRENT CONCEPTIONS OF PATHOGENESIS OF BOTULISM

Moscow SOVETSKAYA MEDITSINA in Russian No 3, Mar 82 (manuscript received 7 Sep 81) pp 62-65

[Article by V. N. Nikiforov and V. V. Nikiforov, Department of Infectious Diseases (headed by Prof V. N. Nikiforov), Central "Order of Lenin" Institute for Advanced Training of Physicians, Moscow]

[Text] An increasing number of articles is appearing in recent years, which deal with various questions of pathogenesis of botulin poisoning, but most of them deal primarily with certain aspects of this problem without dwelling in detail on pathophysiological, histochemical and biochemical disturbances associated with botulism. Thus, foreign authors attribute paresis and paralysis solely to inhibited discharge of acetylcholine in the peripheral end of a motor nerve conductor ("Botulism in the United States, 1899-1977"). But this obviously simplified approach cannot explain other clinical and pathophysiological manifestations of botulism--functional disturbances in the liver and kidneys, changes in catecholamine balance (N. P. Chesnokova and O. G. Astaf'yeva), hyperglycemia, questionable effect of anticholinesterase products, etc.

Heretofore, the main point of application of the pathogenic effect of toxin has raised debates. Thus, R. A. Saltykov et al. failed to demonstrate a direct toxic effect from botulin on tissue cultures (HeLa, mast cells), whereas other authors described such an effect on erythrocytes and leukocytes, which could serve for high-speed diagnostic purposes (E. N. Shlyakhov).

Some selectivity of the toxin is manifested by depression of functional activity of large (physical) motoneurons of the anterior cornua of the spinal cord with concurrent depression of their functions as trophic centers for thick myelinated fibers and virtually intact slow motoneurons, preservation of rhythmic function of neurons of the respiratory center (S. D. Mikhaylova; V. V. Mikhaylov). The mechanism of pathogenic effect of the toxin has not yet been entirely defined; however, the existing data warrant the conclusion that all four types of hypoxia play the leading part in development of botulin poisoning--histotoxic, circulatory, hemic and hypoxic. There is no clearcut line between these forms, since they merge closely at some stage and one type of hypoxia could cause appearance of another type. The data of V. V. Mikhaylov, who established that there is substantial increase in passive ion permeability of large motoneurons for potential-forming ions, depression of protein synthesis and

slowing of axoplasm transport in axons are indicative of the leading role of histotoxic hypoxia in the mechanism of the above-described disturbances.

However, all of the described processes occur in the cell with expenditure of a large amount of energy, and they are oxygen-dependent. Thus, the function of the sodium-potassium pump, which provides for stability of ion balance in the cell, is closely linked with macroerg metabolism and gleans energy from the pentose-phosphate shunt (V. I. Burakovskiy and L. A. Bokeriya). One can obtain analogous increase in passive ion permeability experimentally, by inhibiting of carbohydrate metabolism by end products of glycolysis or inhibiting oxidative phosphorylation (Yu. A. Akimov and M. F. Shuba)--the main route of energy metabolism in cells. In favor of histotoxic hypoxia, with which the cells lose the capacity to utilize oxygen even when its partial tension is high, is the fact that artificial ventilation of the lungs (AVL), which is capable of holding blood oxygenation at the normal level even in the complete absence of spontaneous respiration, does not arrest degenerative processes in large motoneurons.

Progressive acute respiratory insufficiency (ARI) is the consequence of depression of large motoneurons that innervate respiratory muscles, and in serious cases it leads to adverse outcome. Hypoxic hypoxia is secondary here, in relation to the direct effect of the toxin. Development of ARI in the presence of botulism is also potentiated by development of pulmonary atelectases due to hypoventilation and possible obstruction of the bronchi by aspirated vomitus, saliva and food, which is due to paresis of muscles of the larynx, pharynx and epiglottis.

The data of G. A. Akimov et al. (1971, 1972), who observed disturbances in virtually all neurons forming the motor pathway, starting from cortical cells, are not consistent, in some respects, with the data of V. V. Mikhaylov about nonspecific damage to central nervous system cells, in addition to those observed in large motoneurons. Comparable data were obtained by I. Ya. Anosov and T. I. Bulatova, who demonstrated that, within the first 4 h after giving the toxin per os to guinea pigs, in a dosage eliciting clinical signs only after 36 h, there was increase in activity of succinate dehydrogenase and acid phosphatase--enzymes whose activity consistently increases in the presence of hypoxia of any genesis--in cells of the reticular formation near the respiratory center. The total absence of any clinical manifestations of disease at the time of the examination is indicative of the direct effect of the toxin, i.e., histotoxic nature of the above-described disturbances in enzyme activity.

Toxin-induced impairment of energy conditions of cells is confirmed by the experiments of N. P. Chesnokova and G. Yu. Kulyash, who incubated erythrocytes with toxin in vitro. It was shown that, under these conditions, there is considerable depression of ATPase activity and decrease in osmotic resistance of erythrocytes, i.e., impairment of active ion permeability. However, erythrocytes can receive energy directly from the pentose-phosphate shunt, bypassing the usual cytochrome pathway--they have no mitochondria, they are rich in lactate dehydrogenase and relatively resistant to hypoxia and anoxia; and cyanide compounds, whose effect is a typical example of histotoxic hypoxia in structures containing mitochondria, have no effect on oxidation of glucose by erythrocytes (Kh. Iost). Thus, depression of active ion permeability of the

erythrocyte membrane under the influence of botulin toxin could be due to inhibition of enzymes of the pentose-phosphate shunt.

A comparison of this possible mechanism of effects of the toxin on erythrocytes to data about its effects on neurons could lead to the conclusion that the disturbances it elicits are generally in the same direction and manifested by a change in transmembrane permeability, due to limited access of energy into the system of the sodium-potassium pump. In the case of erythrocytes, this effect of the toxin leads to another type of hypoxia, hemic, since increased hemolysis is observed as a result of decrease in their osmotic resistance. It should be added that in some *Botulinum* strains a capacity was demonstrated for secreting in a cultural filtrate hemolysin that is sensitive to the effects of oxygen. This component of botulin toxin is capable of lysing ram erythrocytes and, after being injected intravenously, causes death of mice (M. V. Dalin and N. G. Fish). The foregoing means that hemic hypoxia can be considered to be one of the first and foremost pathogenetic mechanisms of development of botulin poisoning.

Further analysis of the pathogenic effect of the toxin revealed that its influence extends equally to the autonomic nervous system, clinically manifested by dryness of the mucosa, midriasis, reduction of pupillary reaction to light, changes in the cardiovascular system. In a study of the effect of the toxin on the circulatory system, G. Ye. Brill' observed elevation of systolic pressure already at the early stages of poisoning, which was associated with attenuation of depressor vagal influences. This conforms with the data of N. P. Chesnokova (1978) concerning the drastic depression by the toxin of the parasympathetic nervous system on the level of the truncal and sacral regions, the sympathetic nervous system being virtually intact (V. V. Mikhaylov). It was noted that, as in the case with the large motoneurons of the anterior cornua of the spinal cord, AVL did not eliminate even partially the depression of the parasympathetic branch of the peripheral nervous system. However, dissociation of sympathoparasympathetic influence leads to more severe sequelae than could have been expected. It was demonstrated in several works (S. D. Mikhaylova and T. M. Achkasova; N. P. Chesnokova, 1974) that, already at the early stages of botulism, there is a drastic increase in epinephrine and norepinephrine content of virtually all organs and tissues. The effects of catecholamines are well-known, and they consist of inotropic and chronotropic effects on the heart, contraction of arterioles of the skin, kidneys and intestine, dilatation of arterioles of striate muscles and myocardium against a background of spasm of most veins, increased coagulability of blood, stimulation of all types of metabolism with increased oxygen and glucose uptake, faster degradation of phosphate-macroergic derivatives (APT, creatinine phosphate). However, such increase in organ function is not related to greater economy of function, but unjustifiably "generous self-combustion" and rapid depletion of reserves (A. P. Zil'ber). In high concentrations, catecholamines are capable of inhibiting enzymatic SH groups and block tissular respiration, i.e., lead to tissular hypoxia, impair cardiac function to the extent of development of micro-infarction; they can be instrumental in appearance of the syndrome of disseminated intravascular coagulation. Hence, hypercatecholaminemia may not only aggravate the course of any form of hypoxia, but become the cause of some of them. Thus, spasm of precapillary and postcapillary sphincters, as the main mechanism of "centralization" of circulation under the

influence of epinephrine, impairs peripheral perfusion of blood, i.e., leads to circulatory hypoxia, whereas the acidosis, which develops in the region with reduced microcirculation, makes it drastically more difficult for dissociation of oxyhemoglobin--hemic hypoxia develops.

It should be noted that the disturbances in catecholamine balance are not all the same. Thus, in most tissues there is an increase in epinephrine at the stage of development of paresis, with concurrent drop in concentration of norepinephrine, while during the period of development of paralysis these changes are opposite in nature. N. P. Chesnokova (1978) believes that the initial elevation of epinephrine concentration is the result of toxin-caused activation of processes of methylation of norepinephrine. At the terminal stage of the illness, this process is depressed due to development of ARI, and norepinephrine content starts to prevail appreciably over epinephrine. On the other hand, the same author demonstrated a close link between activity of cholinergic processes and catecholamine metabolism, and she concluded that greater or lesser depression of cholinergic processes is associated with activation of catecholamine metabolism.

The depression of peristaltic function of the gastrointestinal tract, in the form of persistent constipation observed at the height of illness, is also attributable to the influence of elevated catecholamine levels. This was proven in the studies of I. S. Kuz'min: the course of botulin poisoning in animals with surgically removed adrenal medulla was not associated with such severe depression of gastrointestinal peristalsis as in the control. Interestingly, AVL not only fails to compensate the disturbances referable to catecholamine balance, but, on the contrary, against a background of elevation of blood oxygen tension during AVL, the intensity of its extraction and utilization in muscles consistently declined, as compared to the same stage of poisoning without AVL (O. G. Astaf'yeva and N. P. Chesnokova). Such progression of tissue hypoxia could be related to excessive accumulation of biogenous amines and their metabolites in tissues, in the presence of AVL, since the latter stimulates processes of norepinephrine methylation.

However, the potentiating effect on development of illness of catecholamines can be considered decisive evidence of their role in development of botulin poisoning. Thus, administration of these substances to experimental animals lowered significantly the MLD of the toxin. At the same time, giving the sympatholytic, reserpine, which attenuates the adrenergic influences on effector systems of peripheral organs, lowers norepinephrine content of the central nervous system and elicits a number of parasympathomimetic effects, leads to depotentiation of the effect of the toxin, which is manifested by an increase in MLD (N. P. Chesnokova, 1978).

Thus, the submitted data speak in favor of the leading role of hypoxia in the pathogenesis of botulin poisoning. All forms thereof (hypoxic, tissular, circulatory and hemic), which are attributable to both the direct effect of toxin and the system of intermediate factors (catecholamines, acidosis, etc.) and are tightly interwoven, elicit at the final stage appearance of the disturbances which, on the whole, determine the symptomatology of this disease.

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METHODOLOGICAL APPROACHES TO DETERMINING EMERGENCY MEDICAL CARE REQUIREMENTS
OF RESIDENTS OF MOSCOW

Moscow SOVETSKAYA MEDITSINA in Russian No 3, Mar 82 (manuscript received
11 May 81) pp 72-75

[Article by P. M. Isakhanov, Moscow Scientific Research Institute of Emergency
Medical Care imeni N. V. Sklifosovskiy]

[Text] Scientific validation of the public's requirements with regard to
emergency care is needed to plan the emergency medical care service in Moscow
at the prehospital stage. For this, it is necessary, first of all, to
determine the objective patterns of requests for emergency care referable to
different age and sex groups according to classes of diseases, individual
diseases and sets of symptoms, as well as the main patterns on receipt of
calls at the emergency station (substation) with respect to time (time of
day, day of the week, ordinary days and days off, months, seasons) and mean
time spent by mobile brigades to respond to calls.

The absence of special studies dealing with the scope and nature of emergency
care in Moscow, scientific validation of indicators of demand for this type
of medical care, as well as mobile brigades with different specialties,
prompted us to investigate these questions.

The scope, nature of emergency station (substation) work, level and structure
of public's requests for emergency care were studied for a full calendar year
by the sampling method (10% sample with $t = 2$, $\Delta = 0.1$), by means of filling
out a specially developed "Card for Emergency Medical Care Calls."

Before starting this study, we had instructive and methodological conferences
with physicians and paramedical personnel at the emergency station (substation)
concerning organization and procedure for filling out this card; the personnel
were provided with specially prepared instructions. All of the tags on the
card were coded; numbers were entered in the charts that corresponded to
each concrete case, and diagnoses were coded in accordance with the eighth
revision of the International Classification of Diseases. Each call involving
a visit to a patient or victim by the emergency station's (substation's) team
was taken as the case unit. We took one 24-h brigade, which responded to
calls in the same ambulance as the gauge of availability of emergency care
to the public. In order to determine the intensity of indicators of requests

for emergency care, we used data on the size and age-sex composition of the population in accordance with the most recent census (1979). We standardized these indicators by the direct method to eliminate the influence of differences in age-sex composition of the residents of different parts of the city on incidence of requests made by the public for emergency care. We took as the standard the age and sex structure of the population of Moscow according to the 1979 census. In all, we gathered, processed and analyzed 200,000 emergency call cards.

Our study enabled us to detect the distinctions of calls for emergency care made by residents of different parts of the city, determine the level and structure of calls according to classes of diseases, main diseases and sets of symptoms, as well as the principal patterns of calls made by different age and sex groups and distribution of calls in time.

To assess the justification of public calls for emergency care, requirements of the public referable to specialized forms thereof, we used the expert method. Experienced specialist physicians performed expertise. In order to provide a unified approach to expert evaluations, we developed appropriate methodological instructions. The results of expertise enabled us to determine the scope of unwarranted requests for emergency care, demonstrate flaws in organization of the work of walk-in and polyclinic institutions, as well as validate the needs of the city's residents for specialized types of emergency care. We used specially prepared questionnaires, which were sent out to certain groups of those who requested emergency care, in order to determine the causes of unwarranted requests for emergency care, rather than visits to polyclinics. In all, we processed 5000 questionnaires.

The study of the influence of different indicators of polyclinic work on the incidence of unwarranted requests for emergency care was made with the use of multifactor analysis.

Time studies occupied an important place in our investigation to determine time spent on responses as a whole and on different elements of the work of the mobile emergency team as related to nature of illness for which the call was made. The results of time studies of mobile regular and specialized emergency station (substation) teams were entered on a specially developed photo-time card.

According to data in the literature (M. A. Messel'; L. B. Shapiro; E. S. Antipenko; Ye. A. Kustova), there is a rather wide gap between minimum and maximum time spent per response. For this reason, to calculate the required number of time measurements, we conducted preliminary measurements in order to determine maximum and minimum time spent on responding to calls using the following formula:*

$$\Delta = \frac{t \cdot \sigma}{\sqrt{n}}, \quad n = \frac{t^2 \cdot \sigma^2}{\Delta^2},$$

*Sepetliyev, D., "Statistical Methods in Scientific Medical Research," translated from Bulgarian, Moscow, Meditsina, 1968, p 140.

where n is the required number of cases, t is the confidence coefficient, σ is standard deviation and Δ is mean error in sample.

We timed 1103 responses by emergency teams at the station (substations). The results of these time studies were processed by the method of variational statistics. We calculated the weighted mean (M), standard deviation (σ) and mean error of weighted mean (m) for all elements of the work of mobile teams related to responding to calls. The obtained differentiated data on time spent by emergency teams to respond to calls were used to determine the needs of the public for mobile teams of different specialties.

In determining the public's requirements with regard to emergency care, we used as the basis the data on actual incidence of calls using the expert evaluations as correction coefficients for frequency of requests. Arrival of calls to an emergency station is an uncontrollable process; the flow of calls cannot, as we know, be limited by directive measures, and all incoming calls must be serviced immediately. For this reason, the existing scope of emergency care to the residents of Moscow was used as the basis for determining their current need for emergency care.

We used the results of expert evaluation of real need for emergency care by the public, in the presence of considerable improvement in the quality of care of the public by walk-in and polyclinic facilities, for planning future indicators of overall need for emergency care.

The scope of specialized emergency care (referable to the team specialties) was determined on the basis of expert evaluation of data pertaining to calls for emergency care, with due consideration of complete satisfaction of patient needs for specialized forms of emergency care.

The public's need for specialized emergency care was determined on the basis of expert evaluation of the need of the public for various specialized forms of emergency care. The actual incidence of rendering specialized forms of emergency care to the city's residents does not reflect the true need for such care. This is attributable to a number of causes: some part of the sick and casualties in serious condition requiring emergency specialized care is serviced by the regular teams; part of the sick and casualties who received specialized care could have been serviced by regular teams without lowering the quality of treatment.

We considered diseases according to requests for specialized and regular teams to calculate the scope of specialized emergency care.

We took into consideration the need of children for narrowly specialized forms of emergency care (cardiological, toxicological, neurological, resuscitation) to estimate the needs of the urban residents for the same types of care. The need for pediatric care was estimated on the basis of requests for emergency care when, according to the experts' conclusion, narrowly specialized care was not needed, but the children required emergency care by pediatricians.

We used the mathematical apparatus of mass queueing theory to determine the public need for mobile teams in different specialties to upgrade the quality

and scientific validation of emergency care planning. We took into consideration the uncontrollable nature of incoming calls, their distribution according to time of day in accordance with the "Programmed" law of Poisson, number of delays and correlation between these factors.

Development of a mathematical model and use of computer technology in planning emergency care make it possible to find the optimum solution in each specific instance. Estimation of the required number of mobile teams for current and future emergency care planning was made according to a specially prepared program used on a type Ryad-1020 general-purpose computer and the software of queueing theory.

Use of this method made it possible to study the scope and nature of work at an emergency station (substations) for a city with population of many millions, determine the frequency of calls as related to sex, age and form of disease, determine the main patterns of distribution of calls in different seasons, months, days of the week and hours of the day, calculate the mean time spent per response by teams and, using the expert method, we were able to validate the indicators of current and future need of the residents of Moscow for emergency care.

Use of a modern planning method--mathematical apparatus of queueing theory--made it possible to validate scientifically the differentiated indicators of current and future needs of the residents of Moscow for mobile emergency teams referable to different specialties.

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CSO: 1840/314

ORGANIZATION OF CONTROL OF VENEREAL DISEASES IN MOSCOW OBLAST

Moscow SOVETSKAYA MEDITSINA In Russian No 3, Mar 82 (manuscript received 15 May 81) pp 81-83

[Article by Ye. V. Verbenko and T. M. Shuvalova, Dermatology Clinic (headed by Prof G. F. Romanenko), Moscow Oblast Clinical Scientific Research Institute imeni M. F. Vladimirskiy, Moscow Oblast Dermatological and Venereological Dispensary (chief physician V. A. Lyuosev)]

[Text] The term "venereal diseases" refers to a large number of various diseases that are caused by a group of heterogeneous pathogens, the property in common of which is that they are transmitted primarily through sexual intercourse and that the pathogen cannot exist for any length of time outside the body.

Venereal diseases include syphilis, gonorrhea, trichomonad involvement of genitourinary organs, soft chancre, venereal lymphogranulomatosis (fourth venereal disease) and granuloma inguinale (fifth venereal disease).

Venereal disease infection occurs through physical contact, most often during intercourse or during pregnancy and labor, from mother to infant, which puts these diseases into a special category of infectious diseases.

In view of the rapid spread and serious consequences to patients and offspring of venereal diseases such as syphilis and gonorrhea, they should be considered as most dangerous infections and it should be a pressing matter to institute a set of preventive measures.

Introduction to practice of penicillin therapy, refinement of methods of diagnosing syphilis and gonorrhea warranted the belief that venereal diseases would be eradicated within a short period of time. However, this did not happen. The rapid spread of venereal diseases made it necessary to take immediate complex steps to control them.

In the article by D. Good, "Diseases Transmitted Through Sexual Intercourse," it is reported that, worldwide, four people contract one of the venereal diseases each second.

Of the two main venereal diseases, the incidence of gonorrhea is 10 times higher than that of syphilis.

According to WHO data, there are three main routes that lead to lowering the incidence of venereal diseases: 1) health education of the public; 2) primary and secondary prevention; 3) training physicians in different specialties in differential diagnostics of venereal diseases.

New methods for a differentiated system of venereal disease control publicity are being developed in accordance with these recommendations, with consideration of sex, age, culture and knowledgeability in health matters of the public. The role of these factors is investigated by means of anonymous polling of different age and social groups. With these questionnaires, it was possible to learn that 86% of those polled know about venereal diseases, their infectiousness and routes of transmission, 80% are properly informed about the early signs of disease. From the same questionnaires, it was possible to determine causes instrumental in infection (alcohol intoxication, loose sex life, careless attitude toward one's own health, etc.). Special lectures were prepared for young people, the adult population and physicians in different specialties with consideration of data obtained after processing these questionnaires, as well as diagnostic mistakes. Special topic evenings are organized on a wide scale, with screening of special movies, poster exhibits, and mass media are used--local radio and local press.

Another route that lowers venereal diseases is active detection of sick cases and contacts at the earliest possible time. For this purpose, several measures are used that involve not only dermatovenereologists, but a wide circle of medical workers and administrative bodies. These measures provide for establishing epidemiological groups for operative disinfection of stricken sites, examination of specified groups in inspection offices, running Wasserman tests on somatic patients, as well as individuals who come in for intercurrent diseases. In particular, obstetrician-gynecologists make a significant contribution to active detection of patients with venereal diseases when they examine pregnant women and patients with various chronic inflammatory processes of the reproductive system. The share of syphilis cases detected when checking cure of syphilis and gonorrhea is growing. A comparative evaluation of the importance and effectiveness of work on active detection of venereal cases revealed that the highest incidence (up to 50.6%) is referable to individuals picked up among the immediate contacts of patients. The group that is next in significance and size (up to 15%) is referable to individuals who are picked up when somatic patients are submitted to the Wasserman test. It is followed by the group of individuals detected when population groups officially subject to check-ups are examined (11.4%). Physicians in allied specialties, chiefly obstetrician-gynecologists, offer appreciable assistance, detecting cases of venereal diseases when patients are seen for the first time. Individuals detected by the militia constitute 2.6% of all actively detected cases.

Aside from the preventive work of dermatovenereological institutions, an equally important factor in the control of venereal diseases is development of new and refinement of existing methods of treating patients with venereal diseases and, first of all, the most serious one--syphilis.

New experimental data have appeared in recent years about the nature and biological distinctions of the pathogens of syphilis and gonorrhea, and this led to

a search for more effective treatment methods. Penicillin has the greatest therapeutic activity. When agents of the penicillin class cannot be tolerated, as well as in the case of resistant strains of the pathogen, use of agents in the group of aminoglycosides of the tetracycline class, macrolides, etc., is recommended.

At the present time, the high therapeutic efficacy of the one-course continuous method of treating syphilis with large single and course doses of penicillin is recognized by all. The only disagreements that arise are related to choice of single dose and cumulative dose of penicillin, as well as methods of treating advanced and seroresistant forms of syphilis.

In this report we have discussed only the principal factors instrumental in lowering the incidence of syphilis in Moscow Oblast in 1979-1980. But this does not mean that we have already exhausted all resources for the control of venereal diseases. This control could be even more successful if, not only public health agencies, but other services and agencies, as well as Soviet and Party bodies, become actively involved in it.

Further refinement of existing and search for the most effective forms and methods of organizing the control of venereal diseases and reliable methods of individual prevention constitutes a pressing task for scientific research institutions.

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HEPATIC LIPOGENESIS IN EXPERIMENTAL BURNS

Moscow PATOLOGICHESKAYA FIZIOLOGIYA I EKSPERIMENTAL'NAYA TERAPIYA in Russian No 3, May-Jun 82 (manuscript received 12 Apr 81) pp 43-46

SLOBODIN, V. B. and KUZNETSOVA, V. A., Chair of Biochemistry, Ivanovo Medical Institute

[Abstract] Radioisotopic methods were used to study hepatic lipogenesis in albino rats with experimental burns covering 25-30% of the body surface. The results showed that in such animals hepatic lipogenesis from acetate and certain amino acids was increased, while that from glucose and pyruvate was depressed. Since lipolysis exceeded hepatic lipogenesis, the net effect was a reduction in serum lipid levels. Figures 2; references 15: 1 Western, 14 Russian.

[340-12172]

UDC 616.61-002.151-39.73

EFFECTS OF PREDNISOLONE THERAPY ON COURSE AND OUTCOME OF HEMORRHAGIC FEVER WITH RENAL SYNDROME

Kazan' KAZANSKIY MEDITSINSKIY ZHURNAL in Russian Vol 63, No 2, Mar-Apr 82 (manuscript received 17 Mar 81) pp 5-7

KUSTARNIKOV, G. K., OSINTSEVA, V. S. and PIMENOV, L. T., Chair of Infectious Diseases, 2nd Chair of Hospital-Base Therapy, Izhevsk Medical Institute

[Abstract] Supportive therapy for hemorrhagic disease with renal syndrome was complemented with prednisolone (30-40 mg/day, reduced to 2.5-5 mg/day with improvement; in patients with cardiovascular insufficiency the starting dose ranged from 80 to 120 mg/day; mean duration of therapy was 12.3 days). The results of treating 40 patients with moderately severe and 30 with severe forms of hemorrhagic fever complicated by renal syndrome showed that prednisolone promoted abatement of toxic symptoms, disappearance of pathologic features in urinary sediments, promoted recovery of normal kidney function, and shortened hospital stays.

[375-12172]

ACID-BASE BALANCE AND ELECTROLYTE METABOLISM IN PATIENTS WITH HEMORRHAGIC FEVER AND RENAL SYNDROME

Kazan' KAZANSKIY MEDITSINSKIY ZHURNAL in Russian Vol 63, No 2, Mar-Apr 82 (manuscript received 24 Mar 81) pp 8-10

CHUKAVINA, A. I., MOTYREVA, A. I. and GORLOV, V. T., Chair of Infectious Diseases, Izhevsk Medical Institute

[Abstract] Acid-base balance and electrolyte metabolism were investigated in 167 patients with hemorrhagic fever accompanied by renal syndrome, ranging in age from 16 to 50 years. The results showed that acid-base imbalance and abnormal serum electrolytes were found primarily in subjects with acute renal insufficiency. Generally speaking, patients with moderately severe conditions were in subcompensated and compensated metabolic acidosis, while patients with a severe course presented with metabolic alkalosis. Mixed respiratory and metabolic acidosis was diagnosed in some patients with both pulmonary and renal insufficiencies. In most of the convalescent patients serum electrolytes recovered normal values, although in a few hyperphosphatemia and hypochloremia persisted 1.5-3 months after the onset of disease. Mechanisms responsible for the acid-base and electrolyte disturbances are complex, but do involve adrenocortical lesions, renal dysfunction, enhancement of catabolic processes, and loss of electrolytes with vomitus. [375-12172]

EFFECTS OF ANTIOXIDANTS ON BURN WOUND REGENERATION

Kiev KLINICHESKAYA KHIRURGIYA in Russian No 3, May 82 (manuscript received 7 Jan 82) pp 13-15

SMORSHCHOK, S. A., YAKUBYSHINA, L. V., SOKOL'SKAYA, V. A., VOLKOV, K. S., KUZIV, O. Ye. and BIGUNYAK, V. V., Chair of Histology, Medical Institute, Ternopol'

[Abstract] Histologic studies were conducted on guinea pigs to determine the effects of sodium selenite and alpha-tocopherol on the healing of experimental burn wounds covering 15-20% of the body surfaces. Sodium selenite (20 µg/kg) and alpha-tocopherol (50 mg/kg) were given parenterally for ten days, beginning one day after the injury and thereafter once per three days until sacrifice. The results showed that inhibition of lipid peroxidation with these agents activated epithelial proliferation, enhanced formation of granulation tissue and angiogenesis, promoted anabolism, and led to earlier healing and scab rejection. Figures 3; references 12 (Russian). [342-A-12721]

NEW COLLAGEN SOLUTION-BASED DRESSING FOR BURN WOUNDS

Kiev KLINICHESKAYA KHIRURIYA in Russian No 3, Mar 82 (manuscript received 11 Feb 81) pp 16-19

GORBATOV, V. M., BABLOYAN, O. O., KOMISSAROVA, L. R., TUZOVA, N. N., ANUFRIYEVA, V. G., DAUROVA, T. T., SELEZNEVA, L. G., DEGTYAREVA, S. M., OSTOLOPOV, V. A., YUDENICH, A. A. and SERGAL', O. S., All-Union Scientific Research Institute of the Meat Industry, USSR Ministry of the Meat and Dairy Industry; Institute of Surgery imeni A. V. Vishnevskiy, USSR Academy of Medical Sciences

[Abstract] Experimental and clinical trials were conducted with combutec-2, a spongiform collagen preparation, as a dressing for burn wounds. The cytological and phatomorphological studies on experimental animals, and clinical trials, demonstrated that combutec-2 constitutes a well-tolerated dressing favoring early healing of second and third degree burns, promotes early epithelialization formation of granulation tissue, and reduces the incidence of keloids. The incidence of keloid formation was 12 out of 52 patients with IIIa-degree burns treated with combutec-2, whereas the incidence in 107 in whom combutec-2 was not employed as part of the therapeutic regimen was 67. Consequently, combutec-2 has been shown to be an effective agent in promoting the healing of superficial burns and warrants more extensive clinical application. Figures 3; references 9: 3 Western, 6 Russian.

[342-A-12172]

HEMOSORPTION IN BURN PATIENTS

Kiev KLINICHESKAYA KHIRURGIYA IN Russian No 3, Mar 82 (manuscript received 25 Aug 81) pp 19-21

VIKHRIYEV, B. S., TERNOVOY, K. S., KUZNETSOVA, L. A., NIKOLAYEV, V. G., BAUTIN, Ye. A., DOLYA, I. A. and SAKUN, Yu. M., Kiev

[Abstract] Clinical trials were conducted on 17 patients with deep burns covering 20-50% of the body surface, employing veno-venous femoral vein shunt. The patients ranged in age from 25 to 50 years. This form of detoxication therapy was found to yield clinical improvement of 2-3 days duration, without any adverse effects on blood chemistries and rapid recoveries of the formed elements (which were slightly depressed by hemodilution). Clinical findings indicate that this therapeutic approach should be investigated further as a viable modality in the treatment of burns. References 2 (Russian).

[342-A-12172]

NEW SCHEME FOR CLINICAL PERIODIZATION OF BURNS

Kiev KLINICHESKAYA KHIRURGIYA in Russian No 3, Mar 82 (manuscript received 20 May 81) pp 54-56

KLYACHKIN, L. M., Chair of Therapy, Medical Institute, Saratov

[Abstract] A critique is presented of the current Soviet periodization of burns and their sequelae, with a proposal for a new scheme based on three principles of classification. These encompass the pathologic process itself (skin damage, formation of necrotic scab, suppuration and loss of scab, granulation, epithelialization), identification of general compensatory mechanisms and decompensation, and general pathologic consequences of the injury.

[342-A-12172]

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COMPUTER-BASED DETECTION OF NONAKHLAZIN-INDUCED CHANGES IN CARDIAC ADAPTIVE RESERVES IN ALCOHOLICS

Moscow BYULLETEN' EKSPERIMENTAL'NOY BIOLOGII I MEDITSINY in Russian Vol 93, No 5, May 82 (manuscript received 25 Jan 82) pp 68-72

KAVERINA, N. V., BERDYAYEV, S. Yu. and MEL'NIKOVA, T. S., Laboratory of Cardiovascular Pharmacology, Institute of Pharmacology, USSR Academy of Medical Sciences, Moscow; All-Union Scientific Research Institute of General and Forensic Psychiatry imeni V. P. Serbskiy, Moscow

[Abstract] EKG manifestations of cardiac function were evaluated in 24 17-46 year old male alcoholics with frequent complaints of severe chest pains, before and after physical stress (isometric support of a 0.5 kg weight with an extended arm for 5 min) and after 14 days of treatment with nonakhlazin (120 mg/day) or placebo. Computer-based histograms of the R-R interval (covering the interval duration mode, amplitude mode of the intervals, and variation range) showed that in patients with alcoholic cardiomyopathy this parameter was more constrained and indicated less functional flexibility than in a group of healthy control men, in whom extensive variations in the time intervals facilitated easy adaptation to a new heart rate to meet the challenge of physical stress. Nonakhlazin induced marked improvements in the EKG patterns, reduced the incidence of extrasystoles, reduced the heart rate to a mean of 80.4 beats/min (vs. a mean of 91 beats/min during abstinence), and normalized the R-R interval histograms. Nonakhlazin appears to potentiate the sympathetic effects on the heart in response to a physical load. Figures 4; references 7 (Russian).

[377-12172]

SEMITHIN SECTION STUDY OF GUNSHOT WOUND HEALING

Moscow BYULLETEN' EKSPERIMENTAL'NOY BIOLOGII I MEDITSINY in Russian
Vol 93, No 5, May 82 (manuscript received 13 Nov 81) pp 113-116

GRIGOR'YEV, V. V., ZAYTSEVA, K. K. and KOSACHEV, I. D., Military Medical
Academy imeni S. M. Kirov, Leningrad

[Abstract] The course of healing of experimental gunshot was investigated on rabbits, using light microscopy and 1-2 μ m thin sections. This use of semithin sections was found to be a convenient method for the evaluation of granulation tissue formation and the identification of the various cellular elements, and thereby to constitute an important adjunct to standard histological procedures. Figures 3; references 8: 1 Western, 7 Russian.
[377-12172]

UDC 616.98:579.841.93]-079.4:616.126-002.1-022.7

DIFFICULTIES IN DIFFERENTIAL DIAGNOSIS BETWEEN BRUCELLOSIS AND SUBACUTE
SEPTIC ENDOCARDITIS

Moscow KLINICHESKAYA MEDITSINA in Russian Vol 60, No 3, Mar 82
(manuscript received 23 Feb 81) pp 44-48

PEREKOPSKAYA, T. I., KALEV, O. F., SKORODUMOVA, N. A., PEREKOPSKIY, I. S.
and PERMITINA, L. V., Chair of Infectious Diseases and Chair of Hospital
Therapy of the Faculty of Therapy, Medical Institute; City Hospital No. 7,
Chelyabinsk

[Abstract] A brief review is presented of the difficulty in differentiating brucellosis from subacute septic endocarditis, which is supported by the presentation of two case studies that focus on the need to differentiate between general cardiovascular pathology in brucellosis and the rather rare complication of endocarditis. The diagnostic difficulties are particularly apparent in patients with long-term rheumatism, and should be suspected by the astute clinician in patients with prolonged fever, chills with perspiration, hepatolinal symptoms, and positive serology and other tests for brucellosis. References 19 (Russian).
[343-12172]

LESIONS OF NERVOUS SYSTEM IN SALMONELLOSIS

Moscow KLINICHESKAYA MEDITSINA in Russian Vol 60, No 6, Jun 82
(manuscript received 20 Jul 81) pp 14-17

KANAREYKIN, K. F., BAKHUR, V. T., ESKIN, M. A. and MANVELOV, L. S.,
Scientific Research Institute of Neurology, USSR Academy of Medical Sciences,
Moscow

[Abstract] The etiology, epidemiology and pathogenesis of salmonellosis are reviewed, with particular reference to involvement of the nervous system. Published work is cited showing neurologic morphologic changes found at autopsy. Lesions of the nervous system vary according to the severity and form of the salmonellosis and are seen clinically as neural disorders resulting from intoxication, headaches, disturbed sleep and dizziness, and meningeal symptoms seen in muscular pain and paresthesia. All neural symptoms occur more frequently and are more marked in children. Isolated cases of suppurative cerebral and meningeal lesions have been found most often in children. Shifts in the EEG in cerebral lesions in salmonellosis remain for long periods following clinical recovery. In cases of cerebral involvement in the disease, Salmonella are found in the cerebrospinal fluid. Therapeutic methods are discussed. References 27: 23 Russian, 4 Western.
[389-9642]

MICROBIOLOGY

UDC 628.34(088.8)

ISOLATION, STUDY AND IDENTIFICATION OF ALPHA-METHYLSTYRENE DEGRADING MICROORGANISMS

Alma-Ata IZVESTIYA AKADEMII NAUK KAZAKHSKOY SSR: SERIYA BIOLOGICHESKAYA in Russian No 3, May-Jun 82 pp 50-53

DZHUSUPOVA, D. B., Institute of Microbiology and Virology, Kazakh SSR Academy of Sciences, Alma-Ata

[Abstract] Twenty strains of alpha-methylstyrene-degrading bacteria were isolated from the waste water of a synthetic rubber plant. Bacteriologic procedures led to the identification of these bacteria as *Pseudomonas* spp., with one definitively identified as *Ps. alcaligines*. All were characterized by the ability to use alpha-methylstyrene as the sole carbon and energy source. References 5: 2 Western, 3 Russian.
[403-12172]

UDC 576.615.858.28

ROLE OF PROTEOLYSIS IN REPRODUCTION OF HUMAN AND ANIMAL VIRUSES AND ANTIVIRAL ACTIVITY OF PROTEASE INHIBITORS

Moscow USPEKHI SOVREMENNOY BIOLOGII in Russian Vol 93, No 3, May-Jun 82 pp 352-362

LOZITSKIY, V. P. and POLYAK, R. Ya., Scientific Research Institute of Virology and Epidemiology imeni I. I. Mechnikov, Ukrainian SSR Ministry of Health, Odessa; All-Union Scientific Research Institute of Experimental Medicine, USSR Academy of Medical Sciences, Leningrad

[Abstract] A literature survey is presented on the significance of proteolytic enzymes in viral replication and pathogenicity, and on the potential therapeutic usefulness of protease inhibitors. Particular attention is accorded to the successful clinical application of epsilon-amino-caproic acid in the treatment of pediatric cases of influenza and other acute viral respiratory infections. References 115: 3 Ukrainian, 43 Russian, 69 Western.
[355-12172]

CYTOGENETIC ASPECTS OF PRODUCTION AND ACTION OF HUMAN INTERFERON

Moscow USPEKHI SOVREMENNOY BIOLOGII in Russian Vol 93, No 3, May-Jun 82
pp 363-381

KHESIN, Ya. Ye., Scientific Research Institute of Epidemiology and Microbiology imeni N. F. Gamaleya, USSR Academy of Medical Sciences, Moscow

[Abstract] The current state of knowledge on the cytogenetics of the formation and action of human interferon is reviewed. To date, 10-12 structural genes have been identified as responsible for leukocytic interferon, and one or two have been implicated in human fibroblast interferon. Currently available evidence points to the location of these genes on chromosome 9, although the possibility exists that either structural or activator genes may be present on chromosomes 2, 5 and conceivably 13. The gene coding for antiviral determinants on interferon-treated cells is on the long arm of chromosome 21, probably cell surface receptors for interferon. The regulatory gene for the antiviral state has been assigned to chromosome 16 on a preliminary basis. Figures 1; references 137: 1 Czech, 13 Russian, 123 Western. [355-12172]

PHARMACOLOGY

UDC: 581.4:577.15/.17

PLANTS AS SOURCES OF BIOLOGICALLY ACTIVE SUBSTANCES

Moscow ZHURNAL OBSHCHEY BIOLOGII in Russian Vol 43, No 1, Jan-Feb 82
(manuscript received 3 Feb 81) pp 65-71

[Article* by G. A. Kuznetsova, Botanical Institute imeni V. L. Komarov, USSR Academy of Sciences, Leningrad]

[Text] Some of the results of studying higher and lower plants as sources of biologically active substances are reported. Data are submitted about products from lower plants--phytohemagglutinin, befungin and others--and from higher plants--balsam, amyloiodine, dimethulene and podo-phylline.

It has been long known that many plants are used in both folk and formal medicine. In this report, it was demonstrated that investigation of plants is promising as sources of biologically active substances and biopolymers (enzymes, polysaccharides and others) for use in medicine and veterinary science, on the basis of the concrete results of studies of higher and lower plants.

The joint studies of botanists and chemists, who make use of the entire armamentarium of the latest advances in systematics, chemistry, physics and mathematics, make it possible to determine exactly the new, most available plant sources of biologically active compounds and to submit them to chemical examination more efficiently. The potential and desirability of developing this direction were first revealed with particular clarity during the Great Patriotic War, when medical balsam recovered from fir resin, which had been developed previously by Prof P. A. Yakimov (1942, 1945), was produced at the BIN [Botanical Institute] at the initiative of N. N. Petrov, academician of the USSR Academy of Medical Sciences (chief surgeon of the Leningrad front) and was a reliable means of suppressing anaerobic infections--gas gangrene--in wounded soldiers on the Leningrad front.

After the war ended, work on improving the quality of balsam continued at the BIN. In view of the great success of antibiotics, it was proposed that usnic acid (an antibiotic contained in many lichens) be added to it. At the present

*Paper delivered by the author at a session of the General Meeting of the Department of General Biology, USSR Academy of Sciences, "General Biology to Serve Medicine," which convened on 18 November 1980.

time this product is being manufactured under the name of sodium usninate, and its former name was binan. However, we should also mention the special value of balsam itself, since it is quite effective and can be used in cases where antibiotics are contraindicated. Concurrently with use of fir balsam, work was pursued to expand its raw material base. A survey of regions in Siberia revealed that one could recover thousands of tons of dry extraction balsam annually from the massive waste remaining in the process of procurement of fir pulp, from the bark, thousands of tons of which are removed from trunks and then burned at storage areas in the forests or at timber-processing combines after barking, thereby satisfying the medical demands. Fir bark contains 9.5-18% tar resin, which can be readily extracted with some solvents. The product, "fir extraction balsam," is approved for extensive use in medicine (Yakimov, 1970).

At the present time, in view of the decree adopted by the CC CPSU and USSR Council of Ministers (13 August, 1979) "On Further Development of Medical Science in Siberia and the Far East," one must continue work to introduce the curative extraction balsam and make utmost use of fir bark waste. Thus, one of the first products proposed by the staff of the Botanical Institute has not lost its importance; on the contrary, it has acquired special practical importance at the present time, a time of intensive development of Siberia and the Far East.

In addition to balsam, several other products of plant origin, which were proposed by the staff of BIN in the postwar years, have been approved for use in medical practice for treatment of various diseases, while others are undergoing biological or clinical trial.

At the present time, work is being conducted at the Botanical Institute for the study of wild plants of the Umbelliferae, Compositae, Malvaceae and other families as sources of biologically active substances differing in chemistry (coumarins, sesquiterpene γ -lactones, polysaccharides and others); lower plants are being studied, as well as higher plants in culture.

When botanists search for plant raw material containing a particular biologically active substance or group of substances in the field, an encountered plant is tested for this substance by means of a qualitative reaction that was previously developed by chemists. Wide use in their work of all types of chromatography and spectral methods makes it possible not only to expedite the process of primary analysis of raw material for detection of specific groups of biologically active substances, but permits procurement of only 1 kg or less (50-100 g) rather than tens of kg of plant raw material to detect the actual source of biologically active substance. This is particularly important at the present time, when many plants are on the verge of extinction and scientists have been confronted with the task of making wise practical use thereof, with due consideration of protection of plant resources.

It must be noted that strict identification of raw material for drugs, from the standpoint of plant systematics, was first started at the BIN and was then developed in our country and others, relieving researchers of many mistakes that could have been made in making chemical analyses of plant raw material.

We describe below the results of some studies that are relevant to medicine.

For many years, a combined [complex] study has been in progress in the Laboratory of Biochemistry of Lower Plants, on the basis of a collection that was created in this laboratory, of the physiology and biochemistry of higher basidial fungi cultivated artificially. This collection is the only one in the Soviet Union of this size and diversity, numbering more than 600 strains of fungi, about one-third of which are edible mushrooms (Nizkovskaya, 1980). Some promising species of Basidiomycetes have been found, the products of whose vital functions can be recommended for use in different sectors of the national economy and medicine. As a result of many years of intensive studies of proteolytic enzymes of higher fungi, a product with rennin action, russulin, was developed, which is being introduced to production of cheeses (Fedorova et al., 1975; Nizkovskaya et al., 1976). It is important to mention that this work was a favorable factor for development of a new drug, rudelin, which is intended for treatment of diseases of the gastrointestinal tract. The active constituent of this drug is acid protease. The staff of the BIN has found the conditions for growing the fungi in a deep culture and laboratory regulations for this have been developed. Rudelin has been proposed as a drug by the staff of the All-Union Institute of Technology of Antibiotics and Enzymes, since they developed the technique for recovering it for medical purposes.

From the practical point of view, some promising results have presently been obtained from studies of thrombolytic activity of enzymes of higher fungi (Falina et al., 1980). In particular, a product was recovered from a culture of the edible mushroom, the winter *Armillaria*, which has demonstrated in vitro that it is as good as the Soviet fibrinolytic of microbial origin, terrilytine. At the present time, this product is undergoing in vivo experimental trials in collaboration with the First Medical Institute imeni I. P. Pavlov (Denisova, Falina, 1981).

We must mention one more of the studies of the Laboratory of Biochemistry of Lower Plants--investigation of phytohemagglutinins of higher fungi, which made it possible to develop a new fungal protein product, whose effect is analogous to that of one of the specific proteins of human blood. This agent can be used in serological practice for blood group typing (fourth). Here-
tofore, proteins for identifying only three blood groups had been found in plants. This product completes development of the set of plant sera that are needed in public health practice to preserve valuable donor blood for medical purposes. This work is being done together with the Institute of Hematology and Blood Transfusion (Gavrilova et al., 1980).

Befungin, which is manufactured by the medical industry and recovered from *Polyporales* fungus, the chaga, has made a good name for itself in medical practice. The chemistry and technology of production of this agent were developed at the BIN. Befungin is used as a symptomatic agent for patients with malignant neoplasms of diverse localization, as well as chronic gastritis and other gastrointestinal diseases (Klyuyev, Babayan, 1979).

We shall discuss some of the results of studying higher plants as sources of biologically active compounds. According to data in the literature, some of their polysaccharides are biologically active substances.

Among representatives of the Malvaceae family, the BIN is studying species of the hollyhock genus, which produce an abundance of mucilage, most of which consists of polysaccharides. Biological (Kozhina et al., 1975) and chemical studies are in progress of polysaccharides of Lenkoranskaya, yellowish-green, pink and other hollyhock varieties (Zaytseva, Kozhina, 1980). Experimental testing of the biological activity of polysaccharides isolated from these plants is being conducted together with the Leningrad Institute of Hematology and Blood Transfusion.

Antibiotic K was isolated from the essential oil of one species of plants of the Compositae family, which was proposed as an antidermatomycosis agent by the staff of the Institute of Microbiology and Virology, Ukrainian Academy of Sciences, and the Botanical Institute. The chemistry and technology of producing this agent are being developed by the staff of the Laboratory of Plant Substances at the BIN, and the product is being manufactured at the Bakhchisaray Essential Oil Plant-Sovkhoz. Chemists have developed a method for checking the quality of the product and clinical trials are in progress in Kiev.

One of the most interesting groups of natural compounds is referable to derivatives of coumarin benzo- α -pyrone, many of which have diverse biological effects and have found application in medicine. The study of native coumarins started in the Soviet Union for the first time at the BIN, in the 1940's, and is continuing today. The reason for investigating them was the fact that plants of the genus *Prangos*, namely feed prangos, was used during the Great Patriotic War to treat equine skin diseases, but the active constituent of this plant had not been studied. In the course of investigation it was determined that feed prangos contains coumarin derivatives that vary in structure and have biological activity. Studies of all species of the *Prangos* genus that grow in the Soviet Union made it possible to identify the structure of new coumarin derivatives and find new sources of biologically active coumarins and furocoumarins (osthole, xanthotoxin and others). On the basis of results of studies, we proposed a modified classification of this group of natural compounds (Kuznetsova, 1967). It was demonstrated that roots and fruit of plants contain the largest amount of coumarins, while biologically active furocoumarin--xanthotoxin--which has considerable photosensitizing activity, is accumulated mainly in the above-ground part of plants (Kuznetsova, 1970).

The studies conducted at the Botanical Institute resulted in an extensive search for new sources of coumarins and investigation of their structure by scientists at many of the research centers of our country. At the present time, several domestic products are being manufactured, which are based on natural furocoumarins: psoralen from *Psoralea corylifolia*, ammifurin from *Ammi dentata*, beroxan from parsnip. These agents are used in the treatment of vitiligo and alopecia areata (Klyuyev, Babayan, 1979).

Together with the Institute of Botany of Belgrad University, we are studying coumarins and essential oils of plants of the Umbelliferae and Labiatae families. As a result, some new sources of biologically active coumarins were found.

The first studies of sesquiterpene γ -lactones started at the BIN led to a search for additional plant sources of a special group of these compounds,

the so-called true guaienolides, which can be dehydrated very readily to "khamazulen" [hamasulene?]. The latter has therapeutic effects on asthma and some forms of allergy. A chemoform of *Artemisia sieversiana* wormwood rich in "true guaienolides" was discovered in Kirgizia. As a result of chemical investigation of this wormwood, a new representative of labile γ -lactones was discovered--sieversin, which readily forms khamazulen when distilled with essential oil, and it was proposed as a drug under the name of dimethulene (dimethyl ethylazulene) (Nazarenko, 1961, 1965). A successful clinical trial of dimethulene was conducted in the Department of Childhood Diseases of the Military Medical Academy imeni S. M. Kirov in Leningrad. At the present time, the product is being tested in the immunotherapeutic clinic of the 63d Clinical Hospital in Moscow. Concurrently, botanists conducted experiments to grow *Artemisia sieversiana* in the botanical gardens of Leningrad, Kiev and Kishinev. Interestingly, together with chemists they established that populations of Sievers wormwood consist of three chemical forms [chemoforms]: 1) matricin type, containing sieversin and matricin; 2) artabsin type, containing artabsin, and 3) those containing no "true guaienolides" (Markova, Nazarenko, 1970). In practice, this led to proposal of a method of gathering wild plant raw material that guaranteed its fitness for isolating dimethylene. The theoretically obtained data indicate that the presence of "true guaienolides" is not a species-specific trait.

In order to lower the cost of this agent, a combined method was developed for recovery of dimethulene from essential oil of *Artemisia sieversiana*, with concurrent isolation of a fraction with oxygen-containing compounds, that were highly rated by perfumers at the Leningrad "Severnoye siyaniye" Factory.

A synthetic agent, isoprine, developed on the basis of a new natural alkaloid, diisopropyl putrescine, from plants of the Leguminaceae family (Ryabinin, 1947), was proposed for use in medicine as a drug that lowers blood pressure. All of the work on identifying the structure of this new alkaloid, development of a method of synthesizing the drug, technology of manufacturing it in industry and method of quality control was done by the staff of the Botanical Institute.

Iodinol, which is based on a complex compound of iodine and polyvinyl alcohol (Mokhnach, 1963), has gained wide recognition. It is very cheap, effective, easy to manufacture and, for this reason, can be introduced on a broad scale to medicine and veterinary science. At the present time, iodinol is manufactured at two plants, and it is used with success for treatment of a number of diseases: chronic tonsillitis, acute sore throat, suppurative surgical diseases and others. At the present time, the Botanical Institute, together with the Institute for Biological Testing of Chemical Compounds (Moscow), is exploring the possibility of wider use of iodinol by mouth to treat acute intestinal diseases.

We must mention one more special feature of this cheap, very effective and nontoxic product for use in veterinary practice in treatment of acute gastrointestinal diseases of livestock and poultry. Iodinol is used with success in a number of major industrial sovkhoses in Leningrad Oblast ("Novyy svet" and others) for prevention of dyspepsia in newborn piglets and for treatment of calves. The following data are indicative of the fact that iodinol treatment is not only effective, but more economical than other products: only 367 rubles

was spent on iodinol treatment of 781 calves and 2510 piglets in 6 months; the cure rate was 96%. In a control group of animals, treatment with other drugs, over 6 months also, cost 2063 rubles. Recovery constitutes 83%, but the animals lost weight during treatment and became susceptible to all sorts of infections (Mokhnach, 1974).

What is particularly important is that iodinol can be used when antibiotics cannot, in cases of disease among both humans and animals, and this is observed rather often. It is of practical importance to continue and expand research on the use of iodinol, which is being conducted at the Botanical Institute together with medical institutions.

Studies of complex compounds of iodine with both synthetic and natural polymers--polysaccharides, starch--revealed that they have unique properties: wide spectrum of antibacterial action, total lack of toxicity when administered via any route to man and animals. A compound of iodine with natural starch--amyloiodine--is being used with success for treatment of dysentery; it also has an antiseptic effect on burns (Mokhnach, 1959, 1974). It was suggested that foods be used that are iodinated with starch and iodide compound to prevent goiter in endemic sites (Mokhnach et al., 1967). Iodinated fruit candy, marmelade and other items are manufactured by several industrial enterprises in the Ukrainian SSR.

The great theoretical importance of these studies is that it was shown, for the first time, that iodine in blue iodopolymers is in a monovalent positive form (Mokhnach, 1974).

We must dwell on yet another product of plant origin--podophylline. It is isolated from roots and rhizomes of *Podophyllum peltatum*. *Podophyllum peltatum* is a long-rhizomed herbaceous perennial (Berberis family), that grows in North America. It has been known as a medicinal plant for more than 200 years. The mixture of biologically active substances isolated from the roots and rhizomes of this *Podophyllum* species and, later on, from the Himalayan *podophyllum*, was included in the pharmacopeia of many countries under the arbitrary name of "podophylline," including the Soviet Pharmacopeia (8th edition) as a laxative and cholagogue.

Special interest in the study of pharmacological and chemical properties of podophylline appeared in connection with publication of a report in the 1940's on use thereof for treatment of condyloma. Immediately, many works were published on the study of the structure of biologically active constituents of podophylline and their effects on plant and animal cells. It was learned that podophylline and some of its constituents have antimitotic effects (their effect on mitosis resembles that of colchicine and colchamine). Products recovered from *Podophyllum peltatum* began to be used in the treatment of skin diseases (skin cancer, eczematoid processes), diseases of the liver and blood.

In the 1950's, we proposed podophylline (Kuznetsova et al., 1959; Lebedeva, 1961) for treatment of laryngeal papillomatosis in children and adults, as well as papilloma of the bladder. This made it necessary to develop not only the agrotechnical conditions for growing *Podophyllum peltatum* in different

parts of the Soviet Union, but investigate the chemistry of podophylline isolated from plants grown on experimental and industrial plantations.

The first experiments with raising *Podophyllum peltatum* in Russia were conducted in the Botanical Garden of Petersburg more than 140 years ago.

The staff of the BIN has done much work on the study of biology and development of agrotechnical conditions for growing *Podophyllum peltatum* in Leningrad Oblast and other oblasts of the Soviet Union (Selivanova-Gorodkova, 1959). It was proven that there is a real possibility of creating industrial plantations of *Podophyllum peltatum*, which is now being raised at the Mostisskiy Sovkhoz in L'vovskaya Oblast (Bogdanova et al., 1980).

Chemical studies of *Podophyllum peltatum* raised in Leningrad and L'vov Oblasts of the Soviet Union revealed that it contains the same biologically active ingredients as podophylline recovered from the roots and rhizomes of *Podophyllum peltatum* that grows in North America. Podophylline contains mainly three groups of chemical compounds: 1) derivatives of 4-aryltetrahydronaphthalene, 2) flavanones and 3) fatty oils. Some derivatives of tetrahydronaphthalene are biologically active: alpha- and beta-peltatines, while the main active ingredient is podophyllotoxin (podophyllin contains at least 40% of the latter) (Kuznetsova et al., 1959; Zozulya et al., 1961). A study of the qualitative composition of podophylline and quantitative amount of the main active element in it--podophyllotoxin--as related to age of the plant and phase of its development made it possible to propose the optimum time for harvesting raw material to produce podophylline from it: plants can be used for commercial purposes in the third year after planting. The best roots and rhizomes are recovered in the spring or fall, when they have a maximum podophylline (3-8%) and podophyllotoxin (up to 60%) content) (Kuznetsova et al., 1959; Kuznetsova, Bogdanova, 1970).

A new method has been proposed for recovery of podophylline, which consists of extraction of roots and rhizomes of *Podophyllum* with chlorine-derivative solvents (Kuznetsova et al., 1960). Experimental production regulations were prepared on the basis of this method. In 1971 and 1980, experimental production series of podophylline were developed at the Zdorov'ye Association of Khar'kov. Podophylline is approved for treatment of papillomatosis. Like the other products of plant origin mentioned above, it is a valuable addition to the arsenal of Soviet drug products.

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ANTIHYPOXIC EFFECTS OF GUTIMIN IN EXPERIMENTAL THERAPY OF ACUTE CHLOROFOS POISONING

Moscow PATOLOGICHESKAYA FIZIOLOGIYA I EKSPERIMENTAL'NAYA TERAPIYA in Russian No 3, May-Jun 82 (manuscript received 23 Mar 81) pp 50-53

KUZOVKOV, G. A., Chair of Military Field Therapy, Military Medical Academy imeni S. M. Kirov, Leningrad, Main Clinical Hospital imeni N. N. Burdenko, Moscow

[Abstract] Studies were conducted on the blood and CSF chemistries of chlorofos poisoned (300 mg/kg, intragastric) rabbits to determine the effects of the Soviet antihypoxic agent gutimin (guanyltiourea) given in combination with atrophine (chlorfos antagonist). Administration of gutimin (50 mg/kg, i.m.) +atropine (20 mg/kg, i.m.) 50-60 min after chlorofos administration led to normalization of blood and CSF chemistries. Normalization of the CSF acid-base equilibrium was due to gutimin-mediated increase in the permeability of the blood-brain barrier to buffer bases, and a concomitant reduction in the lactic acid concentration. The efficacy of gutimin apparently rests on its enhancement of homeostatic adaptation to hypoxia. Figures 1; references 10: 1 Western, 9 Russian.
[340-12172]

UDC 615.276.4.015.44:578.245

OPTIMIZATION OF SCHEMES FOR USE OF INTERFERON INDUCERS

Moscow ANTIBIOTIKI in Russian Vol 27, No 4, Apr 82 (manuscript received 11 Dec 81) pp 40-43

YERSHOV, F. I., MOSHCHIK, K. V., GRIGORYAN, S. S. and FOMINA, A. N., Institute of Virology imeni D. I. Ivanovskiy, USSR Academy of Medical Sciences, Moscow

[Abstract] Studies were conducted on outbred white mice to determine the optimum schemes for the use of (Soviet-made) interferon inducers polyguacyl (polyG:polyC) and bacteriophage dsRNA. Determinations of serum levels of interferon showed that maximum titers with aerosol administration of dsRNA

were obtained in ca. 2 h, with a subsequent rapid decrease and complete disappearance in 6-8 h; intranasal and intraperitoneal administration of dsRNA resulted in equivalent maximum interferon levels in 4-6 h with persistence for up to 24 h. Aerosol administration of polyguacyl led to peak interferon serum level in 2 h with complete disappearance in 6-8 h, while administration by the two other routes led to equivalent peak titers in 4-6 h that persisted for ca. 24 h and showed a decline to half the maximum titer in 48 h. Testing in experimental influenza infections showed that both inducers provided maximum protection when administered intranasally 4 h before viral infection, and in the case of tick-borne encephalitis maximum protection was obtained when the inducers were given intraperitoneally or as aerosols 2-4 h before challenge with the virus. Figures 3; references 2 (Russian). [405-12172]

UDC 615.214.22.015.2:615.31:547.466.3].015.25

MODIFICATION OF FENIBUT AND DIAZEPAM EFFECTS BY GABA RECEPTOR BLOCKER BICUCULLINE

Moscow BYULLETEN' EKSPERIMENTAL'NOY BIOLOGII I MEDITSINY in Russian Vol 93, No 5, May 82 (manuscript received 4 Jan 81) pp 64-65

ALLIKMETS, L. Kh., RYAGO, L. K. and NURK, A. M., Chair of Pharmacology, Tartu University

[Abstract] Investigations on Wistar rats showed that fenibut (beta-phenyl-GABA; 100 mg/kg, i.p.) depressed orientative motor behavior but did not alter the emotional state or aggressiveness, while diazepam (2.5 mg/kg, i.p.) enhanced motor activity and diminished aggressiveness. Bicuculline (GABA receptor blocker; 1.25 mg/kg, i.p.) had no effect on behavior by itself, but potentiated the effects of fenibut and diminished those of diazepam. Given in combination with fenibut, bicuculline had no effect on the rise in homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOCA) induced by the former, but prevented the increase in GABA levels in the limbic structures. Diazepam alone and in combination with bicuculline had no effect on the limbic levels of HVA, DOCA, or GABA. These observations suggest that fenibut and diazepam exert their effects on GABA-ergic receptors by different mechanisms and that this fact underlies the different clinical spectrum of effectiveness of these two tranquilizers. References 9: 3 Russian, 6 Western. [377-12172]

PHYSIOLOGY

UDC: 612.13/.17-06:613.12([47+57]-17)

EFFECT OF INDIGENOUS AND CLIMATE FACTORS OF EXTREME NORTH ON HUMAN CARDIOVASCULAR SYSTEM

Moscow GIGIYENA I SANITARIYA in Russian No 6, Jun 82 (manuscript received
10 Feb 82) pp 79-81

[Article by I. I. Dedenko, B. V. Ustyushin, B. M. Stolbun and O. G. Novikova,
Moscow Scientific Research Institute of Hygiene imeni F. F. Erisman]

[Text] Conditions prevailing at high latitudes, combined with indigenous and climate factors, affect the functional state of the body and, first of all, its principal systems that provide for homeostasis. In recent years, it was found that the cardiovascular system is one of the main ones that is involved in the process of adaptation to unusual conditions of the North (I. S. Kandror; V. I. Turchinskiy; S. G. Krivoshchekov and others). A strain on the cardiovascular system is manifested by elevation of arterial pressure, peripheral resistance of vessels, changes in systolic and minute blood volumes. In addition, one observes disturbances in pulmonary circulation, which consist of hypervolemia, elevation of pressure in the pulmonary artery, increased resistance in the pulmonary circulation system and hypertrophy of the right ventricle (A. P. Avtsyn et al.; L. N. Matveyev and S. N. Medvedev; A. P. Milovanov).

These distinctions of cardiovascular system reactions were noted primarily in adults. At the same time, Zh. Zh. Rapoport, V. A. Neyazov and G. S. Ponomarenko report that the child's circulatory system functions under some strain in the Extreme North: increase in heart rate, significant elevation of minimum and distinct decline of maximum arterial pressure, tendency toward increased tonus of precapillaries, increase in minute volume of circulation and cardiac index. These authors also report that there is a disturbance in processes of self-regulation, and that the cardiovascular system functions in a mode that is not energetically advantageous. Zh. Zh. Rapoport does not consider the demonstrated quantitative changes in hemodynamic parameters to exceed the range of the physiological norm. Conversely, the studies of A. S. Pulikov et al. indicate that there are marked morphological changes in the pulmonary circulation of even newborn infants, and this could not fail to affect the function of the circulatory system later on.

At the same time, the data in the literature do not enable us to fully assess the general orientation of functional changes in the human circulatory system in the North, due to the fact that authors have used different methodological procedures to study children and adults.

Our objective here was to determine the distinctions of the cardiovascular system of individuals living in the Extreme North on the basis of investigation of three occupational groups of adults and preschool children who were born there and had always lived there.

We evaluated the cardiovascular system of 51 construction workers, white-collar workers, mine workers (25 to 30 years old) and 102 children (5-7 years old) attending nursery schools in two cities of the Arctic region at relative rest, using conventional methods: we measured arterial pressure by the Korotkov method, recorded the electrocardiogram in the 12 usual leads, as well as 2 additional ones (zone of right ventricle influx and efflux pathways), rheo-pulmonogram according to Pushkar' and conducted variation pulsometry. We calculated parameters characterizing systemic hemodynamics: systolic and minute blood volumes, cardiac index, mean dynamic pressure, specific peripheral vascular resistance; we computed statistical parameters of variation pulsometry and the parameters of pulmonary circulation.

For this study, we selected essentially healthy men who had no history of cardiovascular, nervous or other system diseases.

Table 1. Parameters of systemic circulation in individuals of different occupational and age groups residing in the Extreme North (M±m)

Parameters	White-collar workers	Construction workers	Miners	Children
Heart rate/ beats/min	75±3,0	60±2,5	72±3,2	86,3±4,1
Mode, s	—	1,02±0,03	0,82±0,01	0,70±0,06
Mode amplitude	—	35,0±4,38	43,0±3,5	21,2±0,2
Variational range, ΔX, s	—	0,24±0,03	0,23±0,02	0,17±0,01
Tension index	—	67,8±15,1	127,8±9,7	116,7±12,0
Arterial pressure, mm Hg				
minimum	83,0±3,7	81,7±4,2	84,0±4,5	68,8±1,4
maximum	135,4±7,8	132,7±6,7	139,0±8,1	109,8±2,0
dynamic mean	107,2±5,2	109,2±6,1	111,5±5,7	82,2±4,2
SPR, dyne·cm ⁻⁵ ·s ⁻¹ ·10 ⁴	480,0±12,3	454,0±13,2	456,5±11,5	224,0±6,6
SPR _a /SPR _n , %	151,2±6,4	149,8±5,3	152,0±5,8	—
Systolic volume, ml	63,9±3,4	66,9±4,1	56,7±3,2	27,1±1,7
Minute volume, l/min	4,23±0,3	4,19±0,5	4,26±0,4	2,38±0,1
Cardiac index	2,71±0,2	2,21±0,3	2,18±0,2	2,95±0,1

Key: SPR_a) specific peripheral resistance, actual
SPR_n) specific peripheral resistance, nominal

Tables 1 and 2 list the functional parameters of the cardiovascular system in the groups surveyed. The features in common of the cardiovascular system of adults were: relative elevation of arterial pressure, increased peripheral vascular resistance, signs of increased strain on the right heart and increased tonus of pulmonary vessels.

In addition to the common patterns referable to the condition of the circulatory system, we also found intergroup differences, which were largely attributable to nature of work and working conditions. Thus, we found a definite tendency toward bradycardia, greater elevation of mean dynamic pressure and specific peripheral vascular resistance [SPR] in construction workers. Analysis of

the cardiac intervals revealed vagotonic regulation of heart rate, as compared to miners working deep underground: mode 1.02 s (0.86 in miners), tension index 67 (127 in miners). Intergroup differences due to occupational factors were also noted in pulmonary circulation. The above-mentioned features in common were more marked in individuals working out of doors (builders), who were exposed to the entire set of indigenous and climate factors. The more significant increase in ejection period, maximum filling of lungs, with more marked phase of slow influx, higher dicrotic index and low velocity parameters (see Table 2) were indicative of a greater volumetric overload on the right ventricle, decrease in stroke volume and precapillary hypertension in the pulmonary circulation.

Table 2. Pulmonary circulation in workers of the Extreme North

Parameters	Construction workers	White-collar workers	Miners
Filling period, s	0,415±0,012	0,35±0,02	0,38±0,015
Maximum filling period, s	0,295±0,01	0,215±0,015	0,26±0,011
rapid influx phase	0,145±0,011	0,11±0,01	0,16±0,02
slow influx phase	0,15±0,02	0,105±0,01	0,10±0,01
Dicrotic index, %	66,35±5,2	60,6±4,7	57,14±5,2
Diastolic index, %	69,4±4,3	67,2±5,1	78,57±6,3
Mean velocity, rapid infl. Ω/s	0,93±0,09	1,25±0,05	1,11±0,02
Mean velocity, slow influx phase, Ω/s	0,345±0,04	0,525±0,037	0,35±0,015

The changes in parameters of pulmonary circulation were less marked in individuals who spent virtually all of their time indoors (white-collar workers).

In miners working in deep pits who are exposed to diverse macroclimate and microclimate conditions, there were signs of relative venous stasis in the pulmonary circulation, in addition to the above-mentioned signs. These changes corresponded to strain on the system of external respiration (I. I. Dedenko et al.).

Decline of systolic and minute volumes, increase in specific peripheral vascular resistance and elevation of arterial pressure were the distinctions inherent in the cardiovascular system of children. The high tension index was indicative of greater activity of the sympathetic branch of the autonomic nervous system and reflected some strain in the system of regulating cardiac rhythm.

The children's EKG showed signs of overload and hypertrophy of the right ventricle, as well as conduction disturbances in the form of a partial block of the right crus of the bundle of His. These changes in conduction found in children are assessed by most researchers (L. A. Butchenko; Zh. A. Teslenko and others) as normal variants. However, we cannot rule out the possibility that in some children the presence of a partial block of the right crus of His' bundle is a consequence of right ventricular hypertrophy.

Special use of partial thoracic leads from the zones of right ventricular influx and efflux pathways enabled us to demonstrate, with great informativeness, signs of overload and hypertrophy of the right ventricle due to changes in pulmonary

circulation. The changes in the cardiovascular system of children of the Extreme North were more marked among those living in an industrial city.

Thus, the submitted data are indicative of change in functional state of the human cardiovascular system in the Extreme North. The features that are specific to residents of the Arctic region are: relative elevation of arterial pressure, increase in peripheral vascular resistance, signs of increased strain on the right heart and increased tonus of pulmonary vessels.

It should be noted that the severity of changes in the cardiovascular system, which retains its general orientation due to the indigenous and climate factors of the environment, is also dependent on living conditions and nature of work. One should take into consideration the demonstrated changes in future assessment of adaptation of the body, regional standards and development of ameliorative measures.

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VITAMIN C ADEQUACY IN SEAMEN CRUISING AT HIGH LATITUDES

Moscow GIGIYENA I SANITARIYA in Russian No 6, Jun 82 (manuscript received 14 Dec 81) pp 78-79

[Article by V. S. Novikov and V. P. Petrov]

[Text] We made a study of vitamin C content of tissues in seamen and efficacy of supplemental intake of ascorbic acid during voyages at high latitudes in different seasons.

The first study was conducted during a 45-day voyage in the fall and the second, during a 30-day trip in the spring. In the first voyage, we examined 28 subjects, 14 of whom received 150 mg ascorbic acid daily during the entire trip; in the second study, we examined 40 people, 12 of whom were given 100 mg ascorbic acid daily throughout the trip. All of the subjects were operators 19-20 years of age, with work tenure of 1-2 years in polar regions. Vitamin C was assayed before, during and after voyages. Hydrometeorological conditions during these voyages were typical ones for the given latitudes and times of year. Prevalence of stormy weather, with swells scored at 5-6 points, was a distinction of the autumn voyage. The hygienic parameters of ship quarters conformed essentially to the standards. Ambient temperature fluctuations constituted 21-23°C and relative humidity was in the range of 62-72%.

Mean ascorbic acid content in the subjects' diet constituted 96.9 mg before the fall voyage and 53.4 mg before the spring one (data obtained by estimation).

We assayed vitamin C of tissues by the method of Rotter, which consists of intradermal injection of 2,6-dichloroindophenol (Tillman's reagent), which is discolored by ascorbic acid. The amount of ascorbic acid in tissues is determined from the rate of discoloration of the "lemon peel" that forms at the site of injection of the reagent. When discoloration occurs in the first 5 min, ascorbic acid level is considered good and if this happens within 6-10 min it is considered satisfactory. If the dye becomes discolored at a later time, the tissue is considered to be deficient in ascorbic acid. In addition, we analyzed peripheral blood by the conventional method in all subjects examined during the fall voyage (Ye. A. Kost and L. G. Smirnova).

The results of the studies conducted in the fall revealed that vitamin C levels were satisfactory in tissues of all subjects before the voyage. During the trip, there was substantial decrease in vitamin C content. Already within

the first 2 weeks, it decreased by 22.3%. This was indicated by the longer time before Tillman's reagent becomes colorless, from 6.40 ± 0.29 to 7.83 ± 0.32 min ($P < 0.01$). Subsequently, ascorbic acid content of tissues continued to worsen, and this was associated with appearance of clinical symptoms of hypovitaminosis (Ya. B. Eydinov and M. S. Seregin).

After sailing for 30 days, satisfactory ascorbic acid content of tissues was found in only 7 people and after the voyage in one. The time at which Tillman's dye became colorless increased by one-half, constituting 15.44 ± 0.80 min. The change in vitamin C content during the voyage can be viewed essentially as the result of effects of climate and geographic factors, as well as hydrometeorological conditions. In particular, seasickness alone is capable of impairing vitamin C balance due to disturbance of resorptive processes in the intestine (R. O. Faytel'berg and T. V. Gladkiy). However, one cannot fail to take into consideration the distinctions referable to the work of seamen, which is characterized by a distinctive work and rest schedule, hypodynamia, sensory deprivation, high psychoemotional tension and continuous exposure to diverse shipboard factors, the possibility of adaptation to which depends on both their parameters and duration of a continuous voyage. Consequently, the demonstrated changes should be interpreted as being the consequence of the combined effect of a set of adverse factors on the intimate aspects of metabolic processes. It can be assumed that, in this case, there is oxidation and increased degradation of ascorbic acid.

Hematological parameters underwent substantial changes in subjects with low vitamin C levels. Changes in the leukograms were characterized by a reliable increase in number of neutrophils and monocytes at the start of the voyage, with subsequent tendency toward neutropenia and lymphocytosis. The changes in absolute leukocyte count were particularly graphic: at the early stage of the voyage it increased from 6430 ± 120 to 7080 ± 150 and at the end decreased to 5940 ± 100 ($P < 0.001$).

In the main group, vitamin C levels did not change during the first month of the voyage and dropped insignificantly toward the end of the trip. However, unsatisfactory indicators of the Rotter test were recorded in only three people. In the rest of the subjects, ascorbic acid levels in tissues were satisfactory. This group presented insignificant adaptive changes in hematological parameters, and they did not differ from background data by the end of the trip ($P < 0.5$).

In the period before the voyage in the spring, ascorbic acid content of tissues was good in 7 people, satisfactory in 21 and unsatisfactory in 12, which was apparently due to a decrease in vitamin C content in their diet. During the voyage, there was no decline in vitamin C levels in individuals who had presented good and satisfactory levels before. On the contrary, we observed an increase in number of subjects with good ascorbic acid levels in tissues.

In the main group, which included subjects with unsatisfactory tissular ascorbic acid assays, there was also improvement of vitamin C levels during the voyage. Already after 2 weeks of vitamin supplement (100 mg/day) tissular ascorbic acid increased appreciably ($P < 0.001$). Rotter's test became satisfactory or good in all subjects, while the time required to discolor Tillman's dye

decreased to more than one-half. After the voyage, these parameters improved even more.

Analysis revealed that the dynamics of vitamin C levels in seamen are different during voyages made at different times of the year. In the fall, ascorbic acid content diminished appreciably, as a result of which a vitamin supplement did not prevent the tendency toward decline of vitamin C levels. In the spring, on the contrary, vitamin C levels increased, while a vitamin supplement prevented hypovitaminosis, even in subjects with unsatisfactory levels of tissular ascorbic acid. Evidently, the more adverse climate and hydrometeorological sailing conditions in the fall elicit a greater strain on adaptation mechanisms, which leads to faster outlay of vitamin C, as a result of which intake of a vitamin supplement in the indicated dosage does not prevent the tendency toward decline of vitamin C in the body.

Conclusions

1. In seamen with good and satisfactory levels of tissular ascorbic acid, there is no decline thereof during voyages at high latitudes in the spring. In the fall, the tissular ascorbic acid content decreases as duration of the voyage increases.
2. In seamen with satisfactory vitamin C levels, adaptation to sailing conditions is more stable, and it is not associated with development of deadadaptation changes in the blood system during the voyage.
3. During autumn sailings, a vitamin supplement is required by all seamen. In the spring, it is desirable only for individuals who present a low level of tissular ascorbic acid.

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EXTENT OF SELECTIVITY OF NEUROGENIC EFFECTS

Moscow GIGIYENA I SANITARIYA in Russian No 4, Apr 82 (manuscript received 1 Jul 81) pp 63-65

[Article by S. V. Speranskiy, Novosibirsk Scientific Research Institute of Sanitation]

[Text] The problem of evaluating selectivity of neurogenic effects is the most difficult one in comprehensive measurements of toxicity. Difficulties appear already with the selection of standard substances and ranking them in an orderly list on the basis of data in the literature (N. V. Lazarev; M. A. Mashkovskiy; V. N. Semenova). With regard to any other type of effect, one can always find a toxic agent that does not strike a given system or organ. There are no substances in nature that do not affect the nervous system, since its function is to integrate other functions, and wherever a "break" has occurred it will inevitably elicit a more or less marked "neurogenic" effect. The effect of toxic agents where there is overt prevalence of an other-than-neurogenic effect must be referred to (rather arbitrarily) as absence of selective damage to the nervous system.

At the present time, we have tested a system of graduated determination of selectivity of neurogenic effects on eight standard compounds. In this series, agents that do not selectively strike the nervous system are represented by dioxane (DO), which is a model parenchymatous poison, and benzene (B), which is a typical "blood" poison. On the opposite pole is overt prevalence of neurogenic effects over all others. We can certainly include with agents of this type tetraethyl lead (TEL), which induces classical encephalopathy, the narcotic acetone (Ac) and psychotropic agent, phenamine (P). Carbon tetrachloride (CCl_4), which is also a potent narcotic and, moreover, a poison used extensively to simulate organic lesions to the CNS [central nervous system] is close to these substances. It, however, is also a model parenchymatous poison, which makes it necessary to put it after TEL, Ac and P in the ranked (in descending order) series. The polytropic toxic agent, ethylene chlorohydrin (ETCH), and diethylamine (DEA), which have a marked, but not absolutely predominant, effect on the cardiovascular system will be in third place in this series, which will appear as follows:

TEL, Ac, P \rightarrow CCl_4 \rightarrow ETCH, DEA \rightarrow DO, B

When working out quantitative criteria of selectivity of neurogenic effects, we used the approach that is common to all studies of "volumetric toxicometry": a criterion that correctly reflects the sequence of agents set in the standard (orderly series) is suitable. There were also several other elements in common: experimental animals (white mice), mode of administration of toxic agents (intraperitoneal) and principle of dosing them, according to which all tested doses could be expressed in intervals [steps] away from LD_{50} , while each successive step corresponded to a dosage that presented a 2-fold difference* (first step $1/2 LD_{50}$, second step $1/4 LD_{50}$, etc.). This method of expressing doses (in steps from LD_{50}) is somewhat unusual, but quite convenient for discussing results and forming criteria. We shall use it in our further presentation.

We pursued our search for a quantitative measure of selectivity of neurogenic effects in several stages.

At the first stage, we took four agents (Ac, ETCH, DEA and DO) and determined their thresholds according to the following parameters: muscular strength (MS), summation-threshold parameter (STP), motor activity (MA) and short-term memory (SM). We previously reported the results of this stage (S. V. Speranskiy, 1977a). There is no need to dwell on them in detail here, but we must note the conclusions that determined the subsequent stages. The thresholds for MA and SM in steps from LD_{50} did not affect in any way the severity of neurogenic effects set by the standard agents. Thereafter, we abandoned estimation of these parameters. The thresholds for muscular strength and STP were found to be close to another and they supplemented one another well; however, when compared to LD_{50} , they too showed very minimal correlation to severity of neurogenic effects of the toxic agents (the difference between extreme representatives on the "axis" consisted of only two steps, i.e., it was 4-fold).

We assumed that the situation could be improved appreciably by replacing the median lethal dose, which was used as the reference point, by another integral indicator of the body's reaction that would be closer in level to the threshold of neurogenic effect of the toxic agent. We expected that, under such conditions, the distorting influence of other distinctions of the toxic effect, other than selectivity of damage to the nervous system, would be reduced and the correlation between thresholds would yield the sought criteria. This led us to investigate nonspecific reactions of white mice.

At the second stage of the study, we worked out a system for evaluating the thresholds of nonspecific effects of the toxic agents according to change in adrenal weight. Our expectations were fully justified: for the four agents mentioned, we obtained a very distinct correlation between neurogenic effect thresholds (MS and STP) and thresholds of adrenal reactions that conformed to the gradation of selectivity of damage to the nervous system set with the standard agents.

However, the method of determining thresholds of nonspecific effect according to the adrenal reaction turned out to be rather time-consuming and required an enormous number of animals. For this reason, at the third stage, we began to search for a different (cheaper) method studying the nonspecific reaction,

*Translator's note: sentence is incomplete in source.

which led us to develop the method of starvation in steps ["fractional starvation"?] (S. V. Speranskiy, 1977b). The nonspecificity of this method was confirmed by the fact that the thresholds determined by it were linear functions of thresholds of adrenal reactions. At this stage, we proposed the first (tentative) classification scale to evaluate the severity of neurogenic effects according to $\text{Lim}_{\text{ns}}/\text{Lim}_{\text{idp}}$, where Lim_{ns} is the threshold of neurogenic effect defined as the geometric mean of thresholds for effects on MS and STP, and Lim_{idp} is the threshold of nonspecific effect by the method of fractional starvation (S. V. Speranskiy, 1977c).

Thresholds of nonspecific and neurogenic effects of standard compounds in steps from LD_{50}

Threshold	TEL	Ac	P	CCl_4	ETCH	DEA	DO	B
Lim_{idp}	23	5	9	14	8	6	9	12
Lim_{MS}	25	14	16	17	14	13	10	10
Lim_{STP}	21	14	15	18	12	12	12	13
Lim_{ns}	25	14	16	18	14	13	12	13
P_{ns}	27	23	23	22	20	20	15	14

Note: P_{ns} is parameter of selectivity of neurogenic effect.

thing but more convenient, we obtain overt distortion of gradation of selectivity of neurogenic effects set by the standard compounds. In this case, we find, for example, that TEL is less selective in attacking the nervous system than DO, while CCl_4 has less selectivity than ETCH. What is the cause of this inconsistency? We believe that we were premature in "discarding" such a parameter as distance between LD_{50} and threshold of neurogenic effect. Indeed, this distance does not unequivocally determine the severity of neurogenic effect. However, along with other distinctions of toxic effects (primarily the width of the range of toxic effect), it includes information about neurogenic selectivity of toxic agents.

At the same time, we overestimated the informativeness of the $\text{Lim}_{\text{ns}}/\text{Lim}_{\text{idp}}$ ratio. We found that it unequivocally determines the severity of neurogenic effect only for the special instance when the thresholds of effects of the compounds according to "nerve" indicators in shares or steps from LD_{50} are close to one another. For compounds with very low thresholds (such as CCl_4 and particularly TEL), there is consistent change in sensitivity ratio between methods of determining MS and STP, and the method of fractional starvation (in favor of the latter). The only solution to this situation is to integrate data referable to both parameters, each of which contains partial information about severity of neurogenic effects of the toxic compounds. The simplest form of such integration is addition (in steps) of two distances: from LD_{50} to Lim_{ns} and from Lim_{idp} to Lim_{ns} . And we consider it more correct to consider

The fourth stage of the study involved expansion of the number of standard compounds for further testing or upgrading of the criterion we found. The latter turned out to be valid, i.e., it was necessary to transform, to define the criterion more.

Data on thresholds of nonspecific and neurogenic effects of eight standard compounds are listed in the Table.

If we try to use the criterion we proposed previously ($\text{Lim}_{\text{ns}}/\text{Lim}_{\text{idp}}$) to express both thresholds in fractions of LD_{50} or difference between Lim_{ns} and Lim_{idp} in steps, which is essentially the same

as Lim_{ns} the lesser of the two thresholds (for MS and STP) rather than the mean for them. This conforms best to the very concept of threshold as minimum dose at which manifestation of toxic effects begins. The result of integration (P_{ns}) is shown on the bottom line of the Table. According to the foregoing, $P_{\text{ns}} = \text{Lim}_{\text{ns}} + (\text{Lim}_{\text{ns}} - \text{Lim}_{\text{idp}}) = 2 \text{Lim}_{\text{ns}} - \text{Lim}_{\text{idp}}$

It is not difficult to see that P_{ns} correctly reflects the series, set by the standard compounds, in order of decreasing severity of selective damage to the nervous system. Consequently, this parameter could be the sought criterion. The following classes of selectivity of neurogenic effects of toxic agents are proposed, depending on the value of P_{ns} : over 22--1st class, 21-22--2d, 19-20--3d, less than 19--4th class. According to this classification, TEL, Ac and P are referable to the 1st class, CCl_4 to the 2d, DEA and ETCH to the 3d, DO and B to the 4th class.

The question logically arises as to whether it is necessary to determine two "nerve" parameters or whether one of them is enough, and if so which one.

There is no question of the high correlation between thresholds of toxic effect according to change in MS and STP. In six out of eight cases, the difference between thresholds was within the range of two steps, and in only two cases it was greater, "in favor" of muscular strength in one of these (TEL) and "in favor" of STP in the other (B). Nevertheless, being governed by STP alone would lead to distortion of gradations set by the orderly series of compounds (TEL would "illegitimately" drop in selectivity class, while the neurogenicity of CCl_4 would be aggravated). If one is governed only by MS, each compound would fall into the same selectivity class as if it were assessed on the basis of two parameters.

We still believe it is more reliable to determine thresholds for both parameters, particularly since they can be examined concurrently, on the same animals; if consideration of STP would not affect qualification of selectivity of neurogenic effects if there is further increase in number of compounds studied, this parameter would, of course, "die off," i.e., it would be excluded from the system of toxicometric measurements.

One must take the following into consideration when using the proposed experimental scheme to determine selectivity of neurogenic effects of toxic compounds:

1. MS and STP are determined in mice dynamically, 1, 3 and 6 h, 1 day and 1 week after administration of the tested compounds.
2. Throughout the experiment, experimental and control animals are kept together, otherwise there is drastic increase in information noise (S. V. Speranskiy, 1971).
3. The data should be recorded without knowing the group to which each animal belongs (otherwise, the hypothesis of presence or absence of effect could have an appreciable influence on the result).
4. MS and STP can be compared to the control, not only at different points in time, but in different observation periods (S. V. Speranskiy, 1974a, b; 1975).

In addition to the experimental set-up described above, which involves graded evaluation of selectivity of neurogenic effects of toxic agents, we developed another, less time-consuming form of experiment, which provides an alternative answer to the same question (S. V. Speranskiy, 1980).

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UDC 612.751.1.015.31.014.46:[577.175/446+577.175.322]-06:612.766.2

EFFECTS OF CALCITONIN AND SOMATOTROPIN ON BONE UNDER HYPOKINETIC CONDITIONS

Moscow PATOLOGICHESKAYA FIZIOLOGIYA I EKSPERIMENTAL'NAYA TERAPIYA in Russian No 3, May-Jun 82 (manuscript received 9 Feb 81) pp 64-67

VOLOZHIN, A. I. and DRUZHININA, R. A., Chair of Pathologic Physiology, Medical Stomatological Institute imeni N. A. Semashko, Moscow

[Abstract] Studies were conducted on the effects of daily injections of calcitonin (10 U, s.c., 10-20 days) and/or somatotropin (0.4 IU) on the femur and alveolar process of unrestrained and immobilized Wistar rats. The results showed that calcitonin promoted osteogenesis and counteracted bone resorption in the immobilized animals, while somatotropin was without a similar effect. However, the effects of calcitonin were more pronounced in the unrestrained animals. Somatotropin had no protective effect on the immobilized animals, and when given with calcitonin negated the effects of the latter in both the freely-moving and immobilized rats. Figures 3; references 7: 1 Western, 6 Russian.
[340-12172]

UDC 616.001.8+612.22.11

EFFECTS OF SHORT-TERM REPETITIVE HYPOXIC-HYPERCAPNIC EXPOSURES ON FUNCTIONAL ADAPTABILITY OF HUMAN RESPIRATORY AND CARDIOVASCULAR SYSTEMS

Alma-Ata IZVESTIYA AKADEMII NAUK KAZAKHSKOY SSR: SERIYA BIOLOGICHESKAYA in Russian No 3, May-Jun 82 pp 68-72

SVERCHKOVA, V. S., LYUBOMIRSKAYA, R. I. and TABANOVA, R. A., Institute of Physiology, Kazakh SSR Academy of Sciences, Alma-Ata

[Abstract] Respiratory and cardiovascular responses to physical exertion (20 kneebands/30 sec) were evaluated on 20-35 year old healthy males before and after a 20 day course of breathing via an additional 1500 ml dead space for 20 min/day. Evaluation of the results showed that breathing via an additional dead space did not present undue stress, with the unpleasant

feeling during such respiration disappearing after 4-5 sessions. After the hypoxic-hypercapnic period of training, the subjects showed superior cardiovascular responsiveness to physical stress, consisting of a smaller increase in systolic pressure, a smaller decrease in diastolic pressure, and essentially no change in the heart rate and pulse pressure. Figures 1; references 7 (Russian).
[403-12172]

UDC 612.822.2.014.46:615.217.34

BIOCHEMICAL ASPECTS OF MECHANISM OF ACTION OF CHOLINOLYTICS ON BRAIN

Moscow USPEKHI SOVREMENNOY BIOLOGII in Russian Vol 93, No 3, May-Jun 82
pp 397-408

KRYLOV, S. S. and SEMENOV, Ye. V., Institute of Toxicology, USSR Ministry of Health, Leningrad

[Abstract] Current knowledge on the mechanism of action of M- and N-cholinolytic agents on synapses is reviewed. It has come to be appreciated that postsynaptic blocking of the choline receptors induced changes in the metabolism of neurotransmitters, in ion transport, and in associated enzyme activities. The release of neurotransmitters from the presynaptic depot due to M-cholinolytics results from the excess Ca^{++} at the presynaptic terminals which is due to M-cholinolytic-mediated activation of the Ca^{++} channels in the presynaptic membrane, and depression of neurotransmitter uptake. N-cholinolytics lead to a preponderance of Mg^{++} over Ca^{++} in the nerve endings and retention or even an increase in neurotransmitter storage. The identity of the presynaptic effects of the M- and N-cholinolytics on the cholinergic and adrenergic synapses suggests that the structural features of the presynaptic membranes and their ion transport mechanisms are quite similar if not identical in the various neurotransmitter systems. References 116: 52 Russian, 64 Western.
[355-12172]

VALIDATION OF HYGIENIC STANDARDS FOR IONIZING RADIATION

Moscow GIGIYENA I SANITARIYA in Russian No 4, Apr 82 (manuscript received 13 Nov 81) pp 48-51

[Article by I. V. Filyushkin and I. M. Petoyan, USSR Ministry of Health, Moscow]

[Text] At the present time, the conception of lack of linear threshold is the biomedical basis of setting hygienic standards for ionizing radiation.* Within the limits of this conception, the indicator of expected yield of carcinogenic effects is found by means of simple linear extrapolation of dose dependence of yield of the same effects of exposure to relatively high doses of radiation, which occurs for different reasons. This approach has been adopted by the International Commission for Radiation Protection (ICRP) and UN Scientific Committee on the Effects of Atomic Radiation (SCEAR).

The humanity of this approach should be considered a positive aspect of such a method of assessing detrimental effects, since underestimation of the actually needed scope of measures for radiation protection of people with systemic use of the linear thresholdless conception is apparently ruled out. Another rather important circumstance is that practical estimates of expected risk of radiation-induced tumors in man are simple to make.

With regard to practical application of the principles of radiation protection, the Soviet standards--NRB-76--generally conform to the recommendations of the ICRP and SCEAR, i.e., they are based on the linear thresholdless conception that is validated by social arguments,** in addition to biomedical data.

Generally speaking, there is a possible alternative approach to setting hygienic radiation standards, which is based on recognizing that there is a threshold to the carcinogenic effect (D_{thr}). With such an approach, lower dosage of radiation should be deemed absolutely harmless. For this reason, the permissible radiation level D_{per} appears to be limited by a purely biological condition ($D_{per} < D_{thr}$) and does not require resorting to

*In this case, absence of threshold formally means that radiation, however low its dosage, increases by a finite (though small) factor the probability of cancer within a man's lifetime.

**By the term, social arguments, we refer to administrative, technico-economical and other considerations.

social arguments. Moreover, the choice of permissible "reserve factors" for different categories of personnel and public would also inevitably be based on arguments of an exclusively social nature.

However, it remains unclear whether it is possible, at least to choose between conceptions for setting standards--based on recognition of a threshold or, on the contrary, absence of threshold of carcinogenic effects of radiation solely on a biomedical basis, i.e., without involving social arguments, at least at this stage.

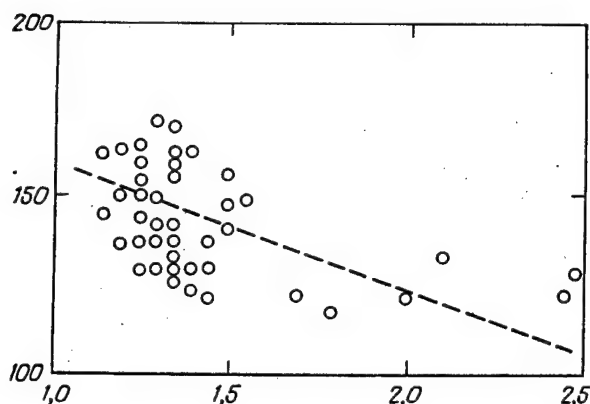
When the question is posed in this manner, it is not the presence or absence of "threshold dose" set within the limits of a given radiobiological experiment or epidemiological study that is significant, but the presence or absence of a threshold to the carcinogenic effect of radiation as a biological phenomenon, on which the observed results are based. It can be shown that this is a basically unsolvable problem within the limits of radiobiological experiments and/or epidemiological studies. The main cause for this is the specifics of interpretation of experimental data concerning the presence or absence of a threshold of carcinogenic effect of radiation. The fact of the matter is that such interpretation requires, in a more or less overt way, the mandatory use of the so-called zero hypothesis, which is deemed valid so long as the results of a given experiment do not refute it conclusively.

A graphic example is interpretation of dose dependence of yield of bone tumors after intake of ^{226}Ra and ^{224}Ra isotopes in man. If the existence of a threshold is taken as the zero hypothesis, both of these functions can be formally recognized as thresholds only by virtue of absence of tumors in people, in whom the accreted mean dosage to the bones did not exceed 10 Gy for ^{226}Ra (Evans) and 0.89 Gy for ^{224}Ra (Spiess and Mays). However, the same data are not in contradiction with the zero hypothesis of lack of threshold. Indeed, if we use a linear thresholdless dose function as the zero hypothesis, the mathematical expectation of number of tumors in the groups mentioned would be 1.9 and 0.8, and this is not enough to refute it with a confidence probability in excess of 0.9; for this, there should be no tumors in groups of people for whom the mathematical expectation of tumors is greater than 2.2. Otherwise, the lack of tumors in a group could be attributed to the effect of purely random factors.

We see that, depending on the choice of zero hypothesis, the results of the same epidemiological study have opposite interpretation with regard to presence or existence of a threshold of carcinogenic effect of radiation.

Interpretation of the results of a recent epidemiological study of mortality due to malignant neoplasms in 49 U. S. states can serve as another example of the role of choice of zero hypothesis in the threshold problem (Fligerio and Stowe). The Figure illustrates data, corrected for age composition, on mortality due to malignant neoplasms recorded among the white population of different U. S. states as related to annual dose of irradiation from all natural sources. We can gauge from this figure visually the formal negative correlation between annual radiation dose levels and the death rate. This is confirmed by quantitative analysis: in 12 states, where the annual dose is

in excess of 1.4 mSv [Sievert = J/kg], the mortality rate is reliably lower than the average for the country and for the group of states with minimal annual dose ($P > 0.999$). If we take the presence of a threshold or even beneficial effects of radiation in low doses as the zero hypothesis, we find that the results of the study cannot refute it conclusively. Thus, an estimate using the linear thresholdless conception leads to a rise of only $2.2 \cdot 10^{-5} \text{ man}^{-1} \times \text{year}^{-1}$ in expected deaths due to malignant neoplasms with a dose rate increase of 1.2 mSv/year. In turn, the value $2.2 \cdot 10^{-5} \text{ man}^{-1} \text{ year}^{-1}$ constitutes only 1.5% of average mortality due to malignant neoplasms in the United States ($150 \cdot 10^{-5} \text{ man}^{-1} \cdot \text{year}^{-1}$). It was impossible to detect such a small increase within the limits of the above study, since variations of mortality indicators referable to malignant neoplasms that are unrelated to a change in annual dose are considerably greater than the rise in mortality expected due to increased exposure of the public. On the basis of the data in the Figure, it can be



Mortality due to malignant neoplasms as a function of annual radiation dose to inhabitants of different U.S. states

X-axis, annual dose of radiation (mSv); y-axis, mortality (in $10^5/\text{year}$); statistical error of estimation of each value is smaller than the size of the points

demonstrated that the mean square deviation of distribution of mortality in states with the same annual dose of 1.25 mSv/year constitutes $13 \cdot 10^{-5} \text{ year}^{-1}$, or 9% of the mean of $150 \cdot 10^{-5} \text{ year}^{-1}$. This could be related to the difference in effects of non radiation factors in different states. At the same time, states with high exposure of the public to radiation occupy an extreme position in the United States according to expressly the characteristics, of which one should expect the maximum effect on deaths due to cancer, and this occurs in the direction of decline at that: lower incidence of bad habits among the public and higher indicators of health status, smaller stratum of people on the poverty level and others (Fligerio and Stowe). Since the expected growth of mortality, according to zero hypothesis (1.5%), is much less than its possible decline due to other factors (up to 20%, according to data in the Figure), this hypothesis can be considered rejected within the limits of

this investigation, while its results cannot serve as evidence of existence of threshold, let alone possible beneficial effect of low doses of radiation, unlike the conclusion of Fligerio and Stowe. Thus, from the standpoint of threshold of carcinogenic effect of radiation, the results of the study of yield of radiation-induced tumors are incomplete--it is necessary to introduce zero hypothesis to interpret them in this aspect. Moreover, the nonspecificity of effects of ionizing radiation as a carcinogenic agent, the equally strong effect of nonradiation factors on observed yield of tumors, the random nature of occurrence of radiation-induced tumors in man and animals, and other causes lead to the fact that judgment of presence or absence of a threshold, when interpreting the results of a concrete radiobiological experiment or epidemiological study, turns out to be predetermined by the previously selected zero hypothesis, i.e., not on the basis of a given experiment.

Indeed, the zero hypothesis for interpretation of experimental data (presence or absence of threshold) is an extra-empirical condition--field of argumentation of its choice and for this reason should go beyond the limits of the experiment on carcinogenic effects of radiation as such. The linear thresholdless conception is the basis of current standard-setting for radiation, and as we know it uses the zero hypothesis of absence of threshold. The absence of threshold hypothesis in this case is contended by "unscientific" considerations of humanity of approach and simplicity of practical estimates of yield of adverse sequelae. However, by virtue of the laws of logic, radiobiological experiments, as well as epidemiological studies that do not refute this hypothesis inevitably constitute the foundation of the linear thresholdless conception.

But, by virtue of the same laws, the linear no-threshold conception and, accordingly, the entire current approach to setting radiation standards appears vulnerable to criticism as being "an administration and not scientific" solution (Mole), and this is often enough for the entire debate to move to an utterly unscientific, in the biomedical context, basis: which approach--the one based on existence of a threshold or absence thereof--is more suitable in the social aspect? Moreover, the existing radiation standard-setting as a whole, as well as accuracy of practical estimates of risk of malignant neoplasm is being also criticized from the theoretical (general biological) points of view, for example, in the works of A. M. Kuzin.

The reason for such a situation is apparently that the linear no-threshold conception appears outwardly to be an excessive oversimplification of the task of estimating expected carcinogenic effects of radiation in low doses. "There has been validation of a general rule in research practice: when a scientist is dealing with an extremely complex problem, at first he simplifies it as much as possible. But one must know how to set the limit of such simplification, beyond which the problem is actually reformulated and, mainly, the objects that the scientist is supposedly working with lose their effective qualities and are transformed into utterly different objects. This limit is not infrequently exceeded in applied problems."*

It appears quite logical that, when solving the problem in question at the early stages (20-25 years ago), validation of the initial no-threshold hypothesis of carcinogenic effect of radiation was limited mainly to social arguments. However, with our present knowledge, the problem can be solved on the basis of more complete and comprehensive examination. A solution may consist, for example, first of selecting the zero hypothesis for interpretation of experimental data exclusively on the basis of biomedical considerations. As we have shown above, the results of radiobiological and epidemiological studies cannot be used by themselves, and for this reason it is inevitable to refer to the aggregate of available information pertaining to etiopathogenesis of malignant neoplasms, but not those directly related to experimental data on the behavior of tumor yield as a function of dosage.

We consider it the most expedient to use, for this purpose, data from experimental and clinical oncology, cellular radiobiology, as well as the corresponding theoretical generalizations. Some of this information could serve as the basis

*Zvyagintsev, V. A., VOPROSY FILOSOFII, No 4, 1977, pp 88-94.

for either direct formulation of "theoretical" prerequisites for absence of threshold of carcinogenic effect of radiation, or indirect, after some mathematical formalization.

The first of these prerequisites is the fact that is recognized in oncology of single-clone nature of most malignant tumors examined, all of the cells of which were found to originate from a single cell that was originally altered. This ensues from biochemical studies of tumors that develop in mosaic hybrid mice (Mintz and Caster), as well as extensive clinical studies of biochemical, genetic and immunological markers of malignant tumors in man (the results of these studies are reflected the most fully in the survey by Fialkov).

The next theoretical premise of absence of threshold is the presence of a linear component in dose functions of yield of all types of radiation-induced effects in cells, and this ensues in particular from recognized microdosimetric theories (I. V. Filyushkin; Kellerer and Rossi). This component is attributable in part to "linear" reactions of part of the pool of proliferative cells to all types of radiation, with regard to yield of all types of effects, down to inactivation of cells (Sinclair).

Finally, the last of the most substantial arguments is that, according to some theoretical generalizations in the area of general carcinogenesis (L. S. Salyamon; V. M. Dil'man; V. S. Shapot; Trosko and Chang), for a tumor to appear there is no necessity for impairment of immunological and/or hormonal system function by radiation: the change to an irreversible form of progression of the tumor occurs against the background of an individual's hormonal and immunological status that does not exceed the range of normal fluctuations for his age. However, the profound immunological and hormonal changes seen in cancer patients are not necessarily the cause of neoplasms, but the result of systemic, in particular immunodepressive, effect of progression of the tumor, as is specially mentioned by V. S. Shapot, for example.

On the basis of the foregoing, the equation for yield of malignant neoplasms as a function of dosage $I(D)$ can be submitted in the following most general form: $I(D) = F[A(D)] \times G(D, P, t, \dots)$, where $A(D)$ is the yield of cells with precarcinogenic changes induced by radiation as a function of dose. This is a non-threshold dose function by virtue of the above-mentioned presence of a linear component of dose functions of incidence of all types of cell damage; $F(A)$ is excessive tumor yield as a function of number of cells with precarcinogenic changes induced by radiation. This is a no-threshold function by virtue of the monoclonal nature of tumors; $G(D, P, t, \dots)$ is a function that describes the role of systemic effect of radiation in carcinogenesis, which can also be a function of dose rate P , individual's age t and others. On the basis of the foregoing, we can demonstrate that the value of this function is not zero with a zero dose of radiation.

We can demonstrate that there is unequivocal presence of no-threshold carcinogenic effect of radiation with this equation, which is the most general formalization of the above-mentioned general biological prerequisites. For this reason, the above prerequisites [or premises] are, in our opinion, sufficient validation of the zero hypothesis of no-threshold nature of carcinogenic

effects of radiation, from the standpoint of which one should analyze the results of relevant experiments and epidemiological studies. To the extent that these data do not refute the zero hypothesis of no threshold, the no-threshold nature of carcinogenic effects of radiation can be considered a biological phenomenon, upon which are based the observed patterns of carcinogenic effects of radiation. A more expanded formulation of general biological (nonempirical) prerequisites for no-threshold carcinogenic effects of radiation and their mathematical formalization, determination of the possible concrete form of functions $A(D)$, $F(A)$, $G(D, P, t, \dots)$ and estimates of parameters they contain from experimental data will be done in the future.

Conclusions

1. The results of any radiobiological experiment or epidemiological study, from the standpoint of demonstration of existence of threshold of carcinogenic effects of radiation, are incomplete; in order to interpret them in this aspect it is necessary to introduce nonempirical premises, in particular, in the form of zero hypothesis.
2. When selecting a zero hypothesis to validate practical setting of standards for ionizing radiation, it is expedient to make a clear distinction between biomedical factors and social arguments.
3. Nonempirical biomedical premises are indicative of absence of threshold in carcinogenic effects of radiation.

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